

Proceedings
of the
Celebration of the Three Hundredth Anniversary
of the
First Recognized Use of Cinchona



Held at the
Missouri Botanical Garden, St. Louis,
October 31—November 1, 1930

St. Louis, Mo., U. S. A.

1931



CAVENTOU AND PELLETIER
Plaques presented by the Société des Quinquinas, of Paris, France

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THE THREE HUNDREDTH ANNIVERSARY OF THE FIRST RECOGNIZED USE OF CINCHONA¹

ANTON HOGSTAD, JR.

Pharmacognosist to the Missouri Botanical Garden

For three hundred years mankind has enjoyed the blessing of the febrifuge properties of cinchona or quinine bark. Nothing is actually known as to the discovery of the febrifuge properties of this bark, but many legends concerning it are to be found in historical archives. One of the most interesting is that some trees in the Peruvian wilds were blown into a pool by the wind, and thereby the water became very bitter, in fact so bitter that the natives refused to drink it. One day a native was seized with a violent fever, and finding no other water to quench his thirst, he was forced to drink of the water from this pool, with the result that he was cured. He then related his wonderful discovery to the other inhabitants of the district, and thus the fame of the febrifuge qualities of cinchona bark became known.

The year 1638 has been generally accepted as the date of the first recognized use of this bark, in which year Countess Ana de Chinchon, wife of the viceroy of Peru, Luis Geronimo Fernandez de Cabrera y Bobadilla, was cured of the intermittent fever. The powdered bark used in this connection had been received from a Spanish corregidor, Don Juan Lopez de Canizares, who having learned of the illness of the Countess, had sent a packet of the powdered drug to Don Juan de Vega, her physician.

Search among the old books at the Missouri Botanical Garden library revealed the fact that eight years earlier this Spanish corregidor had likewise been cured of the intermittent fever by means of cinchona bark, thus establishing the date of the first recognized use of cinchona as the year 1630. It is interesting to note that this finding has been verified by Dr. E. M. Holmes, Ph.C., president of the British Pharmaceutical Conference, in an article entitled, "Three Hundred Years of Cinchona" which recently appeared in the "Chemist and Druggist" (London).

* * * * *

¹ Reprinted from MISSOURI BOTANICAL GARDEN BULLETIN, Vol. 18. No. 9. November, 1930.

Having established the date of the first recognized use of cinchona as being 1630, it seemed fitting and worth while, since the year 1930 marks the anniversary of three hundred years of cinchona medication, to commemorate such a date—to pause in the rush of a busy life and to reflect on the role of a drug that has been official in every edition of the United States Pharmacopoeia since 1820.

The Missouri Botanical Garden, with its many excellent features, including one of the finest and most comprehensive of libraries, a lecture hall unique in character, display rooms, conservatories, etc., presented much as an ideal setting for a gathering of scientists. Accordingly, invitations were extended to scientists, including the leading quinologists, over the world, to participate in such an international gathering. The preliminary plans called for a symposium covering all phases of a botanical, chemical, pharmaceutical, and pharmacological nature, relative to the drug cinchona. It was likewise deemed advisable to bring together what perhaps would prove to be the most comprehensive collection of cinchona barks, their alkaloids, salts and derivatives, as well as photographs, books, etc., that had ever been shown at any one time in the history of a single drug of our vast vegetable *materia medica*.

The response was more than gratifying. From Java journeyed Dr. M. Kerbosch, Director, Government Cinchona Estate and Cinchona Experimental Station at Tjinjircean, Pengalengan, Java, having been accorded a four months' leave of absence by the Java Government. To-day Doctor Kerbosch is recognized as the world's leading authority on the cultivation of cinchona trees, for from the trees under his personal supervision comes 97 per cent of the world's supply of the bark.

From Maarssen, Netherlands, came Dr. A. R. Van Linge, president of the Nederlandsche Kininefabriek, who occupies the responsible position of head of the so-called Dutch Quinine Monopoly. During the summer of 1929 the Missouri Botanical Garden was visited by the son of Dr. Van Linge, who, during a world tour with his wife, stopped off in St. Louis to inspect the Garden. When informed of the proposed Cinchona Tercentenary Celebration the younger Van Linge remarked that he felt sure

that his father would gladly coöperate in such a remarkable undertaking. The result was that this gathering was honored by the presence of this noted quinologist.

Germany was represented by Dr. Karl Merck, president of E. Merck, of Darmstadt, manufacturers of fine chemicals since 1668. The City of Glasgow, Scotland, sent their personal representative, Mr. W. D. Besant, Director of Parks and Botanic Gardens of that City.

A number of noted American quinologists were in attendance. Among them were Dr. George D. Rosengarten and Mr. Joseph Rosengarten, Jr., of the well-known firm of Powers-Weightman-Rosengarten (now merged with Merck & Co., Inc., Rahway, N. J.), which was the first to produce quinine on a commercial scale in this country. Quinine was produced in Philadelphia by this firm in 1823, three years after it had been isolated from cinchona bark by two French scientists, Pelletier and Caventou. Mr. G. W. Merck, president of Merck & Co., Inc., was likewise present. Other guests included Dr. Torald Sollmann, professor of Pharmacology, Western Reserve University; Dr. Kenneth F. Maxcy, University of Virginia, an authority on malarial fever; Dr. Wilbur L. Scoville, dean of American pharmacists, from Detroit; Dr. Edward Kremers, the volatile oil authority and phytochemist, from the University of Wisconsin; and Dr. George Dock, of Pasadena, California, formerly of St. Louis.

Following is a program of the events:

PROGRAM

CELEBRATION OF THE THREE HUNDREDTH ANNIVERSARY OF THE FIRST RECOGNIZED USE OF CINCHONA

Friday, October 31—Saturday, November 1, 1930

Saint Louis

FRIDAY, OCTOBER 31

10:00 a. m.

Assemble at the main entrance to the Garden (Tower Grove avenue and Flora place). Viewing of the Chrysanthemum Show and trip through conservatories.

10:30 a. m.

Exhibition of books, pictures, crude materials, and drugs pertaining to cinchona.

11:00 a. m.

Assemble in the "Library and Museum" Building.

Address of Welcome.....Director George T. Moore

4 PROCEEDINGS TRICENTENARY CELEBRATION OF CINCHONA

"THE HISTORY OF CINCHONA"

The Drug.....	Professor Leo Suppan St. Louis College of Pharmacy
The Chemical.....	Dr. Edward Kremers University of Wisconsin
The Medicinal Use.....	Dr. George Dock Pasadena, California
Dr. John Sappington, Pioneer in the Use of Quinine in the Mississippi Valley.....	Professor Robert J. Terry Washington University School of Medicine

1:00 p. m.

Luncheon at the Garden

2:00 p. m.

"THE CINCHONA INDUSTRY OF JAVA"

Dr. M. Kerbosch
Director, Government Cinchona Estate and Cinchona
Experimental Station
"Tjinjirean," Pengalengan, Java

"THE PHARMACEUTICAL PREPARATIONS OF CINCHONA"

Dr. Wilbur L. Scoville,
Detroit, Michigan

"MINOR ALKALOIDS OF CINCHONA BARK"

Mr. Frederic Rosengarten
Philadelphia, Pennsylvania

"THE CINCHONA ALKALOIDS IN MEDICAL SCIENCE"

Dr. Torald Sollmann
Western Reserve University, Cleveland, Ohio

"THE PRESENT CONCEPTION OF THE ACTION OF QUININE IN MALARIA"

Dr. Kenneth F. Maxcy
University of Virginia

7:30 p. m.

Trustees' Banquet, Hotel Jefferson

Mr. George C. Hitchcock

President Board of Trustees, Missouri Botanical Garden, Presiding

Speakers:

Dr. C. E. Caspari
Dean, St. Louis College of Pharmacy
St. Louis, Missouri

Mr. W. D. Besant
Director of Parks and Botanic Gardens,
Glasgow, Scotland

Representing Pharmacy

Representing Botany

Dr. George D. Rosengarten
Past President of American Chemical Society
Malvern, Pennsylvania

Representing Chemistry

Dr. A. R. Van Linge
N. V. Nederlandsche Kininefabriek
Maarssen, Netherlands

Representing Industry

SATURDAY, NOVEMBER 1

10:30 a. m.

Assemble at the Garden to view Library, Herbarium, and special exhibits.

11:30 a. m.

Leave Museum Building (Cleveland avenue gate) for Missouri Botanical Garden Extension, Gray Summit, Missouri.

1:00 p. m.

Luncheon.

2:00 p. m.

View orchid seedlings and collections. For any who desire it, trips will be arranged to various parts of the grounds.

3:30 p. m.

Return to city.

8:00—10:00 p. m.

Reception at Director's residence.

In the address of welcome by Dr. George T. Moore, Director of the Missouri Botanical Garden, attention was called to the importance of the work of the vegetable kingdom from a humanitarian point of view, as well as the need of commemorating such a date as 1630, the date of the first recognized use of cinchona.

Professor Suppan's paper dealing with the history of this interesting and important drug represented beyond a doubt one of the most comprehensive papers on this subject ever prepared. Professor Suppan spent many months in intensive investigation at the Missouri Botanical Garden, reviewing all of the literature in the various languages.

Mr. Frederic Rosengarten of Philadelphia, being in Europe at the time, his paper on the "Minor Alkaloids of Cinchona," was read by his brother, Dr. G. D. Rosengarten. This paper dealt at some length with the alkaloids cinchonine, cinchonidine, and quinidine, the latter having gained considerable popularity during the past few years as an alternate drug with that of Digitalis in

the treatment of auricular fibrillation. In addition to these three alkaloids, the substance designated as chinoidin was likewise discussed, in which it was pointed out that this substance apparently has many uses as yet unknown.

In discussing the chemical aspects of cinchona, Doctor Edward Kremers reviewed the many pitfalls and complications in the path of the phyto-chemist, as well as pointing out the need for more intensive phyto-chemical research in the future.

Doctor George Dock, formerly of St. Louis, reviewed the medical aspects of the bark, for the most part dealing with the many interesting points relative to its history.

The paper by Doctor Robert J. Terry, on the life and activities of Dr. John Sappington (1776-1856), of Arrow Rock, Missouri, was of especial interest, owing to the fact that through the endeavors of Doctor Sappington, quinine was introduced in the Mississippi Valley in the treatment of malarial fever.

Dr. M. Kerbosch, of Java, presented a very comprehensive picture of the entire cinchona culture industry, and also explained the true purpose of the so-called "Dutch Quinine Monopoly," which is to the effect that this organization is extending every effort to distribute quinine as cheaply as possible for the millions of persons suffering from malarial fever. As stated previously, it is to be remembered that one-third of the population of the world is affected with malarial fever. The paper was supplemented by motion pictures of cinchona culture, prepared especially for this celebration. They were remarkable in every respect, and brought to those interested in this subject the first depiction of every stage in the culture, collection, and preparation of this important drug.

From the dean of American pharmacists, Dr. Wilbur L. Scoville, much was learned about the galenical preparations of this drug, as well as the many problems that the manufacturer of cinchona pharmaceutical preparations has to face every day. Simple percolation is no longer the only problem. It is essential to prepare these pharmaceutical preparations in such a manner that they will retain their efficiency, as well as to eliminate the objectionable features of sedimentation. Doctor Scoville exploded the old-time theory of slow percolation, stating that in the case of cinchona extraction a rapid percolation was far superior.

Dr. Torald Sollmann, the noted American pharmacologist, dealt with the cinchona alkaloids in medical science. The paper was replete at every point with clear-cut facts as to the role of the cinchona alkaloids in modern medical practice. It was interesting to learn from this noted pharmacologist that the branch of pharmacology known as chemo-therapy did not have its origin in the monumental and classic work of Ehrlich on the salvarsans but rather on the discovery of cinchona in 1630, for to-day quinine represents one of the few specific medicines.

The paper dealing with the present conception of the action of quinine in malaria, by Dr. Kenneth F. Maxcy, of the University of Virginia, was a comprehensive review of this vast and complicated problem. Apparently there is much yet to be learned of the mode of action of quinine in the treatment of malarial fever, for this problem, like others of a serological nature, involves the complicated study of blood chemistry, together with an appreciation of its colloid-chemical aspects.

The scientific program occupied the morning and afternoon of Friday, October 31, and a portion of the morning of November 1.

The Trustees' Banquet, on the evening of Friday, October 31, proved to be a most delightful occasion, at which time three hundred guests were entertained. Mr. George C. Hitchcock, President of the Board of Trustees of the Missouri Botanical Garden, was toastmaster for the occasion. It will be noted from the program that Dr. C. E. Caspari, dean of the St. Louis College of Pharmacy, spoke in behalf of Pharmacy; Mr. W. D. Besant, of Glasgow, Scotland, for Botany; Dr. G. D. Rosengarten, of Philadelphia, for Chemistry, and Dr. A. R. Van Linge, of Maarsen, Netherlands, for Industry.

The trip to Gray Summit, Missouri, where the Missouri Botanical Garden maintains an extension of 1600 acres, and where is housed the world's greatest collection of orchids, was a most enjoyable occasion. Two motor busses were chartered for the trip. The fall colorations of the oaks, sumacs, and other shrubs and trees were at their most gorgeous, and afforded the guests an excellent opportunity to note the autumnal beauty of the State of Missouri. After a delightful repast served at the Administration Building, the delegates inspected the collection of orchids. Elinor

Alberts Linder, Orchidologist to the Missouri Botanical Garden, then explained the various steps in the growing of orchids from seed. Her talk was supplemented with the display of orchid seedlings that had just recently been exhibited at the meeting of the American Orchid Society, Washington, D. C.

The Tercentenary Celebration of the first recognized use of cinchona was brought to a close by a reception held at the residence of the Director, on Saturday evening, November 1, at which time friendly greetings were exchanged and many new friendships formed.

The lower floor of the Henry Shaw residence, now devoted to a collection of historical objects, was utilized for the various cinchona exhibits—exhibits that represented the most comprehensive collection of cinchona bark and its products ever assembled in the past three hundred years of cinchona medication. Through the courtesy of Merck and Company, Inc., logs of cinchona trees of varying ages with barks attached, quills of the bark, a bale of ground cinchona bark, roots, branches, etc., had been imported from Java for this occasion. In addition to the above items, this firm exhibited a complete list of cinchona alkaloids, their salts and derivatives, both in crude and purified forms (pl. 2). The Mallinckrodt Chemical Works, St. Louis, as well as the New York Quinine and Chemical Works, New York City, likewise exhibited fine collections of cinchona alkaloids and their salts.

From the Kinabureau of Netherlands was imported a unique set of posters telling the story of quinine in relation to the treatment of malarial fever (pl. 3). In addition to these posters a large oil painting, entitled "Anguish," depicted a person dying of malarial fever at the base of a pile of human skulls, and a skeleton with the wings of the mosquito hovering above.

The Société des Quinquinas of Paris, France, sent for the occasion two plaques of Pelletier and Caventou, discoverers of quinine (pl. 1).

One of the most interesting of all exhibits was the historical relics of the late Dr. John Sappington, of Arrow Rock, Missouri, loaned by the Daughters of the American Revolution (pls. 4-5). This collection included Doctor Sappington's saddle bags, carpet bag, medicine chest, agreement of sale for 10,000 boxes of Sap-

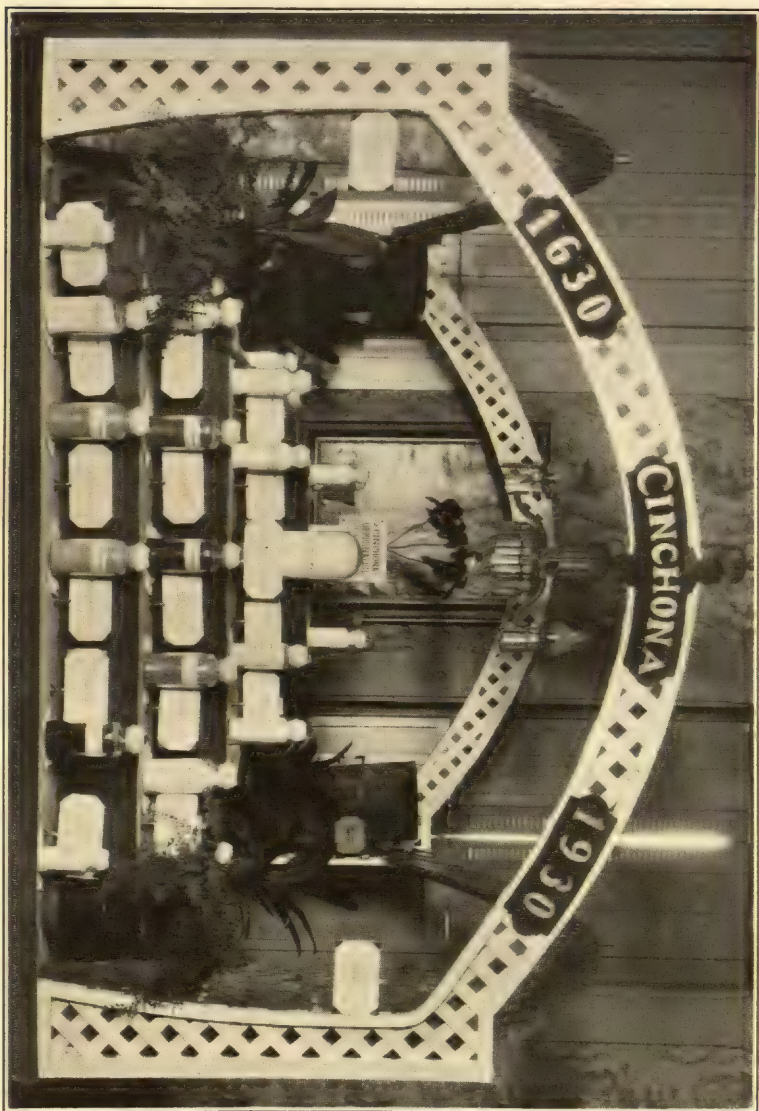


EXHIBIT OF MERCK & CO., INC., SUCCESSORS TO POWERS-WEIGHTMAN-ROSENGARTEN CO.,
1905-1927, POWERS & WEIGHTMAN, 1818-1905, FIRST TO MANUFACTURE QUININE IN THE UNITED
STATES, 1823.



EXHIBIT OF PROPAGANDA MATERIAL OF THE KINABUREAU OF NETHERLANDS
A, heading; B, painting "Anguish"; C-F, posters for Dutch East Indies, G, for Jugoslavia, H, Algeria and Morocco;
I-L, calendars; M, disc for Siam; N-W, books and circulars about malaria and quinine.

ington's Antifever Pills at 60 cents per box, and his prescription book, in which was noted that he charged for both mileage and professional call in those early days. An entry for January 31, 1838, shows that he charged \$4.00 for 80-extract of cinchona pills.

Dr. M. Kerbosch brought with him from Java a most interesting collection of cinchona barks, fruits, and seeds, specimens of cinchona branches, as well as an excellent collection of herbarium specimens of many species of cinchona. He likewise exhibited the method of germination of cinchona seeds, and various forms of animal life that are destructive to cinchona trees.

The Missouri Botanical Garden displayed herbarium specimens and an interesting set of books from the library dealing with all phases of this remarkable drug. The St. Louis College of Pharmacy loaned some books for this exhibit, as did Dr. George Dock, of Pasadena, California.

An added attraction which the Garden offered the guests was the Chrysanthemum Show, which was especially rushed along in order to be in readiness at the time of the celebration.

All in all, this celebration was a most unusual gathering in many respects. It brought together for the first time in the history of this important febrifuge drug the leading quinologists throughout the civilized world. As stated previously, it also afforded an opportunity of displaying the most comprehensive collection of cinchona and its products from the seed to the living plant, as well as all the barks and the many products derived from them. Much was learned of the many hardships endured by those who undertook to search for the source of this remarkable tree in the Peruvian wilds. In a kaleidoscopic manner we were carried over a period of three centuries, during which time was revealed a story replete with points of interest at every turn in the road. We were likewise informed of the many problems confronting the phyto-chemist and pharmacologist in their quests for remedial agents to alleviate the sufferings of mankind. Also, we were told of the true intent and purpose of the so-called Dutch Quinine Monopoly—information that has changed our opinions of it in many respects. We likewise learned much relative to the perseverance of the Dutch, to whom all credit is due for keeping alive an industry that some years ago seemed doomed, owing to

the fact that the market price of quinine was far below the cost of production. When other countries turned to more profitable pursuits, the Dutch kept on, with the result that to-day quinine—the remedial agent *par excellence* for malaria—is to be had throughout portions of the world.

Is it any wonder then that at the close of the Trustees' Banquet in the Gold Room of Hotel Jefferson the guests arose in silence as the orchestra rendered "Wien Neerlandschbloed"—the National Anthem of Netherlands? It was a just tribute to these noble people tendered in the presence of its two official representatives, Doctors M. Kerbosch and A. R. Van Linge, who had traveled thousands of miles to be present at this auspicious gathering.

TRUSTEES DINNER, MISSOURI BOTANICAL GARDEN

Mr. George C. Hitchcock, President of the Board of Trustees, presiding.

THE TOASTMASTER: Ladies and gentlemen, as president of the Board of Trustees of the Missouri Botanical Garden, it gives me great pleasure to welcome you here to-night, on the occasion of the celebration of the Three Hundredth Anniversary of the first recognized use of cinchona bark as a medicine.

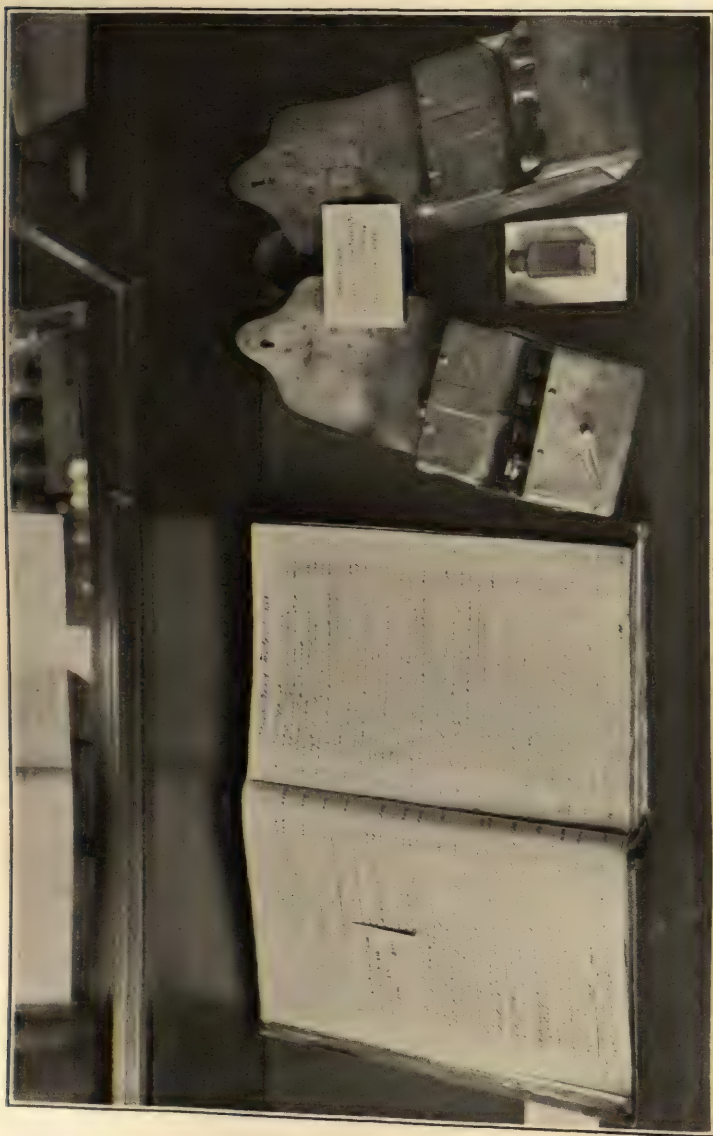
First and foremost, I wish to express the great gratification and appreciation of the Board, to our guests, who have come from foreign lands to honor us with their presence. Dr. Kerbosch, who has come from Java, this afternoon gave a most interesting talk, illustrated with moving pictures, of the industry in Java, and his contribution will be a significant one in the proceedings which the Garden expects to publish. Dr. Van Linge, on my right, comes from Holland. Mr. Besant, on my left, comes from the University of Glasgow. It is a great tribute to the work which the Botanical Garden is trying to do, to have these gentlemen here to-night, and we appreciate it greatly.

I know you will be interested to know that we have received the good wishes and congratulations from botanical gardens in many parts of the world—from Japan, Switzerland, England, Kew Gardens, and a number of other educational institutions and scientific institutions in England; the Pasteur Institute in France; the Botanical Gardens in Brussels and in Vienna. It is a most

SOME OF THE RELICS OF DR. JOHN SAPPINGTON

Included are agreement of sale for 10,000 boxes of Sappington's Antifever Pills, his medicine chest, surgical instruments, photographs of The Old Tavern at Arrow Rock, Missouri.





DR. SAPPINGTON'S PRESCRIPTION BOOK, AND THE SADDLE BAGS

FROM WHICH, TRAVELING ON HORSEBACK, HE DISTRIBUTED THE FIRST QUININE USED IN THE MISSISSIPPI VALLEY.

encouraging thing for those who are charged with the responsibility of carrying on the great work established by Mr. Shaw under his will.

The dinner to-night is given pursuant to the terms of his will, whereby a certain sum is set aside for a dinner to the Trustees and their guests, literary and scientific, patrons of the natural sciences. As I look around among you to-night I am confident that each guest is endowed with every qualification prescribed by Mr. Shaw's will for attending such an occasion as this.

Mr. Shaw was an Englishman, and I think the activities and the work of the members of the Board have been described by a fellow countryman of his, in the words of the Lord Chancellor, when he sang,

"When Wellington thrashed Bonaparte,
As every child can tell,
The House of Lords did nothing in particular,
And did it very well."

(Laughter)

Our function is that of the House of Lords. Under Mr. Shaw's will the Trustees are empowered to appoint a director. It expressly provides that we should not interfere with him in any way, which means we are to abstain from all botanical knowledge. I must confess that I have violated this in one respect. I have read one book which was written by Oliver Herford some time ago; it is called, "How to Tell the Birds from the Wild Flowers." (Laughter) I have not permitted any of the other Trustees to read it, because I think it might interfere with their duties. (Laughter)

The first speaker to-night on the program is from St. Louis, Dr. Caspari, representing Pharmacy, and it gives me great pleasure to call on Dr. Caspari. (Applause)

DR. C. E. CASPARI: Judge Hitchcock, ladies and gentlemen: I esteem it a very high privilege to be able to felicitate on this occasion the Missouri Botanical Garden, and Dr. Moore, together with his associates, for having done what they have done in bringing about this celebration on the three hundredth anniversary of the use of cinchona and its products.

It seems eminently fitting that this celebration should have taken place in St. Louis under the auspices of the Garden, because for some years particular attention has been paid to the growing of medicinal plants at the Garden, also to a study of the production of medicinal plants and, on behalf of pharmacy, the school which I represent having been closely affiliated with the Garden in this work, I am very happy to see it culminate in this celebration.

With respect to the connection between cinchona and pharmacy, it might perhaps be well to ask what pharmacy is to-day compared with what it was, we will say, one hundred years ago, or perhaps a little more, and in doing this I ask you to banish from your minds for a moment the conception which you naturally have of the up-to-date pharmacy of to-day, the corner drug store.

Pharmacy to-day still means considerably more, and stands for a great deal more, than the ordinary public supposes. The same type of research work is being followed in pharmacy as in other professions, and that is entirely aside from the commercial aspect of the profession. Work is being done, not only in the United States but all over the world, the civilized world, in trying to find out the uses, new uses, perhaps new combinations, of medicines for the betterment of mankind.

One hundred years ago the pharmacist was almost in the position of the research chemist of to-day, and if we glance back and review some of the work that was done at that time by pharmacists and not by chemists, we are surprised. Scheele, in Sweden, was a pharmacist; he was one of the discoverers, one of the co-discoverers, of oxygen, and identified it as an element, together with Priestley, in England. These two men had no knowledge of each other's work. We did not have an Atlantic cable in those days; we did not have the radio; we did not have the mail service that we have; and it was a year or two before these men knew that each had discovered oxygen independently. Scheele was an humble apothecary; he also established the identity of chlorine.

Dumas and Liebig, two of the greatest chemists we ever had, were considered to be too stupid to be pharmacists; they started

as pharmacist's apprentices, but were so clumsy and ignorant it was decided they were unfit for that profession and therefore they became mere chemists. (Laughter)

You heard this morning, in Dr. Kremers' paper at the Garden, that the identity of quinine was established by Pelletier and Caventou, and in this beautiful menu which we have this evening you will see a picture of a monument erected to the pharmacists who discovered quinine. It was a pharmacist who first isolated morphine from opium, Sertuerner. It was a pharmacist who first discovered the element of iodine. So pharmacy has really played a very important part in the development of chemistry, particularly that side of chemistry which has been applied to medicine.

We must pay tremendous tribute to the Dutch, who have practically transported the cinchona industry from South America to Java, and who, by careful cultivation and breeding of the cinchona plant, have succeeded in raising the alkaloidal content from perhaps five or six per cent to sixteen, seventeen, and eighteen per cent, and at the same time have very materially increased the amount of quinine in comparison with the cinchonidine, cinchonine, and quinidine, which are the three other important alkaloids occurring in the bark with quinine.

For a number of years, cinchona bark was termed Peruvian bark, but I think the time has come when we should now call it Javanese bark, rather than Peruvian bark, because the world's supply comes practically from Java, thanks to our friends in Holland.

Perhaps some of you saw to-day a full-page advertisement in all the St. Louis newspapers, of the tremendous amount of quinine and other cinchona alkaloids which are being used in St. Louis. I jotted down, after having indulged in a few arithmetic processes, some figures as to the number of doses of quinine, considering a dose to be five grains (I mean quinine and the associated alkaloids), which emanate from St. Louis in the course of a year, and I found there are 218,750,000 grains of quinine used in St. Louis by proprietary manufacturers, by manufacturing chemists who resell, by jobbers and by retail pharmacists, corresponding to 43,750,000 doses of quinine.

In view of that fact, I think we might reverse the statement which is frequently made about dogs, that their bark is worse than their bite—I think in this instance the bark is distinctly better than the bite. (Laughter)

It might be interesting to note that efforts were made some years ago, approximately seventy-five to eighty years ago, to synthesize quinine, that is, to prepare it synthetically in the laboratory and at a cheaper cost, with a view to displacing the natural product and selling it considerably more cheaply. A man in England, who was identified with this attempt, a very capable chemist, W. H. Perkin, did not succeed in synthesizing quinine, but he did succeed, without intending to do so, in synthesizing the first synthetic dye that we had, namely, "mauve" or "magenta"; and about 1852 was the time that was done. Perkin himself perhaps did not realize the importance of his discovery, but the Germans did, and shortly after that a man by the name of A. W. von Hofmann left Germany, went to England, associated himself with the work that Perkin was doing and, after having learned his method of work, went back to Germany. That was the beginning of the establishment of that tremendous line of aniline dyes which rival the rainbow in hue and color, for which Germany has been famous ever since, the first dye having been made in England and the whole industry having been developed as a result of that, in Germany.

This attempt to synthesize quinine is not unlike the attempts that have been made to synthesize many other natural products and, in many instances, that have been successful. The synthesis of indigo, which was formerly a product of plant life and now is made almost exclusively synthetically, has rendered possible the development of large areas of land, particularly in India, for cultivation of potatoes, which serve the Indian race far better than the cultivation of madder from which the natural indigo was prepared.

Much more could be said, but perhaps at the risk of tiring you, concerning the connection of the pharmacist, the professional pharmacist, with the development of cinchona products, but, as you all know, quinine is one of the few specific medicines that are known; it is a specific for malaria, and many patent medicines

have appeared on the market, claiming to control or to cure malaria.

We have a very beneficent influence in Washington, in the Board of Food and Drug Control, which supervises the labeling and the statements made by patent medicine manufacturers, and it is noteworthy that this Bureau of the Department of Agriculture has so regulated the sale of reputed remedies for malaria that it now insists that every such preparation shall contain a dosage, a minimum dosage of sixteen grains per day, over a period of eight weeks, in order to be beneficial in its remedial action upon malaria.

I mention that simply to show that it is not possible, in this country at least, to overstate the claims for a drug like quinine and its alkaloids, the products of cinchona, because our government controls that in a very satisfactory and a well-acting method, and to-day there is practically no cure or alleged cure for this disease, malaria, which is not under government supervision and thus being required to contain the required amount of the alkaloids per dose, and advertising the fact that the medicine must be taken for a certain length of time.

That all has to do with pharmacy. Without boring you any further, I want to express again my appreciation of being allowed to come here and congratulate the Garden, through its Director and its Board of Trustees and its associate members, on this great accomplishment which we are celebrating here this evening. I thank you. (Applause)

THE TOASTMASTER: Among the illustrations which appear in the "Program" of to-night's meeting you may have noticed the photographic reproduction of the statue of the two pharmacists, Pelletier and Caventou, who contributed so much in respect of the use of quinine. How different is the spirit manifested in that statue from the one which was erected in connection with the discovery of ether! My knowledge of medicine is equal to my botanical knowledge, but the tradition is that a man named Jackson discovered ether and another doctor, whose name escapes me at the moment, discovered it, unbeknown to the other, at the same time, and when a statue was proposed to commemorate this discovery, they did not propose to have both men on it, so the legend read, "To the Memory of E(i)ther." (Laughter)

The next speaker comes to us from abroad, Mr. W. D. Besant, the Director of Parks and Botanic Gardens, Glasgow, Scotland. Mr. Besant. (Applause)

MR. W. D. BESANT: Judge Hitchcock, ladies and gentlemen: At the very outset, I would like to express the very great pleasure it gives me to be here, and the honor that has been shown to me by the Trustees and Director of the Missouri Botanical Garden in inviting me to participate in the ceremonies now proceeding.

You will notice by the program that I am representing Botany. I make no pretension to be representing Botany; I am here representing the Botanic Gardens of Glasgow, and I would like to say that the city of Glasgow asked me to convey their greetings and wishes for the success of the ceremony now proceeding.

The Glasgow Botanic Gardens have had various communications and exchanges, and I had the pleasure, some five or six years ago, of showing your Mr. Pring some of our gardens in Glasgow. I can still look back with great pleasure to Mr. Pring's visit to Glasgow.

I have listened to-day with very great interest to all the lectures that have been given. I have learned more in one day here about cinchona than I knew all the rest of my life, but there is one little thing that I did notice: not one of the speakers mentioned the work that has been done by the botanical gardens in the introduction of cinchona. Now, we recognize that the scientists have done a very great deal, but a great deal has also been done by botanic gardens, by experiments, grafting, not only that, but in distribution of cinchona seeds and plants, and also the sending of men to various parts of the world to establish and maintain cinchona plantations. I think this probably refers particularly to Kew Gardens in England; they, I think, have done probably more than any other botanical garden in this direction.

While speaking of Kew, the Chairman intimated that he had greetings from Kew, but as an old "Kewite" myself, two or three days before I left home I received a letter from Kew asking me, when present here, to convey personally greetings from the staff of Kew Gardens to the gathering here and again wishing the ceremonies every success.

Kew has done much, and I think Kew did practically everything, in connection with the introduction of cinchona into India. It is a long story, the introduction of cinchona into India, much too long to go into in detail to-night, but I glanced over it and culled a few notes of what Kew did in the introduction of cinchona, and I may just refer to it here now.

One of the most successful of Kew's achievements was the introduction of cinchona from Peru to the hill country of India. In 1859, Clements R. Markham was entrusted by the Secretary of State of India, in conjunction with Sir William Hooker, then Director of Kew, to make the necessary arrangements for collection of cinchona plants and seeds in South America.

In due course, after many hardships, seeds and plants were packed in Wardian cases—you all know what Wardian cases are: they are greenhouses in miniature in which the plants are packed in the soil they have grown in and forwarded to their destination—and dispatched to Kew. The plants did not get there for some time, then a portion of them were again packed in Wardian cases and transmitted to India. In those days the journey to India might be anything from eight to ten weeks, so it was a great achievement to be able to send live plants all that way, packed in Wardian cases. The remainder, which were not in such good health, were kept in Kew and forwarded as occasion served, not only to India but to Ceylon and other colonies.

The first sowing of imported seeds in India took place early in 1860, and by the spring of 1861 a large supply of plants and young seedlings was established in the Nilgiri Hills. For this work, Mr. McIvor, an old Kew man, at that time the superintendent of Government Gardens, deserves great credit, as it was his practical knowledge and skillful methods which led to such valuable results.

In 1860 it was stated that the Indian government spent over 40,000 pounds in the purchase of quinine for Bengal alone. For many years past it has been possible for anyone to purchase an amount of four grains in any post-office in India. When it is remembered that quinine is the best remedy for malaria fever, it will be realized how great a boon the cheapness of it has been to dwellers in the tropics. Quinine is largely used in Great Britain and is now about one-twentieth the price it was in 1860.

The introduction of cinchona into India is solely due to the efforts of the Botanic Gardens of Kew. Kew still maintains its belief in quinine, at least it did in my time. The students in the tropical areas were very much afflicted with colds and generally run-down feelings, so the authorities at Kew conceived the idea of placing a jar of quinine in each of the sheds, and when the students felt they were "off-color," they took a dose of quinine. Whether it was good or bad for them, I do not know, but I think the students were inclined to take a little too much of it, particularly the Scotchmen, who felt there was something going for nothing. (Laughter)

While speaking of the Scotchmen, perhaps a little story in connection with quinine would not be amiss. A small boy was sent by his mother to the drug store, to purchase six pennyworth of quinine. He duly went into the shop and asked for his six pennyworth of quinine. The man looked at him, a little chap who could hardly look over the counter, and he said, "My lad, what do you want six pennyworth of quinine for?" The reply was pat: "For tu'pence." (Laughter and applause)

THE TOASTMASTER: The next speaker is Dr. George D. Rosengarten, Past President of the American Chemical Society, Philadelphia, representing Chemistry, and I take great pleasure in introducing Dr. Rosengarten. (Applause)

DOCTOR GEORGE D. ROSENGARTEN: Mr. Chairman, honored guests: When Dr. Moore thrust this unexpected honor upon me, I accepted reluctantly and only when he said that I might talk to you informally, so I trust you will forgive my lapses. I expect everything, in a way, is a matter of relativity anyhow, and I found "relativity" is a term that is as old as Methuselah. I suppose it must be, because Methuselah was a very old man. At all events, when Sir Isaac Newton was taking that very pleasant nap in his apple orchard, on a very balmy summer afternoon, an apple fell on his head, which started him speculating; and that apple was very much harder than most apples, so Sir Isaac, in his prophetic mind, said, "Einstein." (Laughter)

Now, my very good friend, Dr. Caspari, stole some of my thunder; I was going to tell you about Liebig, and about Perkin, and

by the way, I really think that pharmacists in England are still chemists. (Laughter) So Liebig, being a pharmacist and eventually a fairly good chemist, had among his students, Hofmann. I am going to correct Dr. Caspari on this a little bit, because Hofmann afterwards taught in London, and one of his students was Perkin. It was in 1857 when Perkin came across that black mass; he thought it was ink or some other smear like that, and did not realize what he had until the next morning when he saw that the color was fast on the color tube.

I was going to reminisce on that a little bit, but, as I said, Dr. Caspari took my thunder away.

Anyhow, Liebig and Hofmann were trying to synthesize quinine and the witness to that synthesis was given by Wöhler when he synthesized urea. So you might trace down from that cinchona chewy ink to the synthesis of quinine, the great dye industry that now holds the world. It does not take much imagination to take that along, and we did not realize, the inkers did not realize, what great benefit they were giving to humanity when they found the effects of cinchona bark.

At all events, quinine, up to perhaps a little more than two decades ago, was the only chemical which in modern parlance would be styled under the term of chemical therapy. Wöhler, in his work, carried that idea on further, and we all realize the benefits his great accomplishments have given to mankind.

Now, I really suppose the most inspiring thing in chemistry is its history. Primitive man carried on a great many methods in the way of science, and he was an unconscious chemist. The thought of the history of chemistry has been indelibly given to me by my beloved friend and teacher, Dr. Edgar Smith, who placed a great deal of weight upon, and gave his students every opportunity to follow, the history of chemistry. Even the Phoenicians, when they built their fire on the sandy beach (I imagine they must have been trying to brew some toddy), protected the flame with limestone and they would use glass; again, they were unconscious chemists, and perhaps they were happier in those days than we are now, because they had good toddy then and they had the glass at the same time. (Laughter)

As we go down further through the history of chemistry, we

come to the alchemist. The alchemists, of course, in a way, tried to fool their clients. With the transfusion of base smears and a great deal of hokus pokus, they tried to put over on everybody the magic things, and things that the ordinary human being cannot understand were all used to their gain, but, as a matter of fact, through those dark ages the evolution showed that things went on in an orderly sort of way, and then the mind grasped that, and from the days of the early chemists that evolution has been carried on.

Now, in a way, we started as alchemists; the rest of the chemists practicing nowadays are alchemists in a way, of a different kind perhaps, because now the chemists will take ill-smelling wastes and turn them into delicate perfumes; they will take the most virulent poisons and turn them into cures; they will take lost matter and make very useful matter out of it. As a matter of fact, chemistry stares you in the face in every direction; you cannot get away from it; from the moment we see the light until after we die chemistry is there; it benefits us, it helps us in every way, takes care of our comforts, and if we realize that chemistry really has only become active in the last 150 years, and think of the potentialities it carries so far to this day, and that it is only in its infancy, we must realize the multitudinous directions to which chemistry still will be extended, so that is still beyond our comprehension. (Applause)

THE TOASTMASTER: The next speaker is Dr. A. R. Van Linge, from Holland. Fundamentally, I think Dr. Van Linge is an optimist. I was speaking to him about the depression, the temporary industrial depression, which prevails in the United States at the present time, and his reply was, "As long as the body feels pain, you are alive—that is all right." (Laughter) I take great pleasure in introducing Dr. Van Linge. (Applause)

DR. A. R. VAN LINGE: Mr. Chairman, ladies and gentlemen: About six months ago, our friend, Dr. Moore, asked me to speak here at this meeting, for five minutes, on any subject. I said, "All right," and now I see that he put me down as representing Industry. Of course, I have done nothing else but work in quinine, so I will have to talk about the quinine industry. You all

know, at least the pharmacists do, that the quinine industry has always been a silent industry. There was not very much talk about that business; you did not like to tell everybody, but now I see I have to talk about it, and I must talk, because I agreed to do so. But you also will understand that, being always in the silent game, it never has been possible for me to talk about quinine at a banquet. Really, I must confess that this is the first speech in public I ever made in my life. (Applause)

I gladly accepted Dr. Moore's invitation to come here to St. Louis, because this town has a very good record in my memory. I like it very much. I was much surprised, last Wednesday evening, I think it was, when I read in the St. Louis Star an article questioning why you should make such a fuss about a product that is made in a foreign country; and as I say I was surprised to read it, because I could have thought that myself.

I am so much at home in St. Louis; I see a Dutch name on every corner, and I rarely meet a man or lady who does not tell me that her grandmother or grandfather came from Holland. If you will forgive me, I did not think of being in a strange town, and we hope if you are ever in Holland, you will have the same feeling and be at home in our country.

At first, I felt angry that my ancestors gave up New Amsterdam, that they gave up their hold here and kept Java, but on thinking it over, the rates of the telephone from here to Amsterdam are about four times as high as the telephone rates from Java to Amsterdam. So, I can see how far-seeing these old gentlemen were, and moreover I think they would never agree with you on the exclusive use of water as the only drink in this country. (Laughter)

Gentlemen, I now must come down to the Industry. I think Dr. Kerbosch has made you very familiar with the growth of cinchona. If you go to Java, I think you will see some very nice cinchona plants. There are already enough, so you need not try growing them. I will tell you something out of my life, how it happened I became a quinine maker, and I think none of you will ever believe how it happened.

I was a student and our very fine and old professor said, "It is a shame that Holland produces all the cinchona bark and then

has nothing to say about the manufacture and sale of quinine made from that bark, and it is to you young men to remedy that situation." We all said, "Yes," but nobody thought about doing it.

After I graduated, I became an assistant director and worked in the laboratory. One of my old friends was our first director in Holland, and he helped a lot in making the cinchona industry in Java a success. He was not married; he was very lazy and could not move very well, but each month he went to the dock. At first nobody understood why it was, but the old man was thirsty and he refused to pay the duty on the alcohol he used in his laboratory, so every time he went he got a little extra alcohol for his own use. One time it was such bad weather that he sent a note asking if the professor could not send somebody to bring the alcohol, and I did the smuggling. I did it very often in winter, and through that little business of "bootlegging" I came in contact with our director. We became very great friends, and he told me all that he knew about the chemistry of quinine, and that decided my fate. From that moment, I was very much decided to become a quinine man, but it only came through a bootlegging business, you see. (Laughter)

I graduated in 1894, and a year afterwards I got an offer from a company in Java to build a factory and a plantation there. The value of the bark was so low that the cost of shipping to Amsterdam could not be paid so the company decided to have a man there and make quinine from this bark. They offered me a very nice salary—sixty dollars a month, and a very nice little bamboo house, such as you have seen in Dr. Kerbosch's pictures, and my old friend Van Gorkom said, "Young man, you are a fool if you accept. You are a graduated engineer and you are a graduated doctor of chemistry, and you must not accept a salary of sixty dollars a month and a bamboo house. That is not enough."

Of course, I am not a financier; he said it was a shame, so I talked it over with a young lady I knew very well also interested in chemistry, and she said, "I think you could do very nicely in a bamboo house in the mountains in Java, with sixty dollars a month. You would not have any expense from coal, you could

burn the wood from the cinchona. It is quite likely you could save money there." I asked her if she would share the bamboo house, and she said, "Yes, I will." So I said, "All right," and she became Mrs. Van Linge.

We lived three years in the hills of Java among the tigers and snakes, and Mrs. Van Linge always said that she, of course, had most of the trouble. I had my work, and she had to stay at home and look after our daily bread. That was not so much, because very many days we could not get it. But, after all, when we think about it, it was a glorious time. There were tigers and snakes in plenty, but we never saw many of them.

Typhoid fever and malaria came, and we were very much worried, so we decided to go to Berlin, where I took over the management of the Berlin factory. We succeeded in making our products, and we could not sell them. It often happens here in this country, you make a thing and find it difficult to sell. For us, it looked rather disastrous, and we did not know what to do. So, one morning, I received a letter from this country, from this town, St. Louis, with a big rosy baby on the letterhead. The letter came from the Paris Medicine house, in St. Louis, and asked me if we were willing to make a contract with them for a supply of all the cinchona products.

I showed that to my directors and they said, "That must be a joke. No serious men could send a letter in such an envelope, and you must not take any notice of the letter." I thought about it, and I decided to write to the Paris Medicine Company, and I said I would be pleased if they sent somebody to Germany. Then Mr. Seely, from this town, thirty years ago, started this trip and came to my home, and at once we became great friends. We made the contract with the Paris Medicine Company and have that contract now. That has really become the beginning of the Javanese growing of cinchona.

Afterwards, I came here and Mr. Seely took me by the arm and took me over the United States, to every pill maker he knew, and said, "I am not satisfied if you do not buy his quinine." So, we came to Parke-Davis and other people here and succeeded in selling them this product.

So, you all know that I am very glad indeed, instead of ora-

tions about the Botanical Garden in St. Louis, to have the occasion to speak on quinine, and I think the dinner has been arranged very nicely. I therefore thank the Botanical Garden, and especially Dr. Moore, from the bottom of my heart, for the occasion he gave me.

In retiring out of business at the end of the year, I think it is my duty to thank all my American friends for the support and friendship they gave me in the building up of my business. Ladies and gentlemen, I sincerely thank you. (Applause)

THE CHAIRMAN: Dr. Van Linge told you about his experience in a bamboo house at sixty dollars a month, in Java. That experience has resulted in the company with which he is associated and the government acquiring 90 per cent of the total product, which is worth mentioning.

I cannot let this evening pass without paying a well-deserved tribute to our Director, Dr. George T. Moore, to whose ability, untiring energy and far-sighted wisdom the Missouri Botanical Garden is indebted for the very substantial contributions, as the Trustees believe, it has been able to make not only to Botany but its allied sciences as well. (Applause). As an illustration, I may tell you confidentially as it were, that the date given in respect of the discovery of the practical use of cinchona bark has varied. Some people say this anniversary should be celebrated a few years hence; one of the letters expressed regret that we had gotten ahead of Holland in celebrating this anniversary. It is simply due to our Director's forehandedness and, in exercising that quality, he would not hesitate at all to anticipate history. (Laughter)

In conclusion and in honor of our guest from Holland, I will ask you to rise, while the orchestra plays the Netherlands National Anthem, after which we will adjourn.

Music:—"Wien Neerlandschbloed."

ADDRESS OF WELCOME

GEORGE T. MOORE

Director of the Missouri Botanical Garden

Distinguished guests, ladies and gentlemen:

We are met here to-day to glorify a plant product. Plants, whether they be used for food, clothing, or shelter, as a drug or decoration, always have been and always will be the most important natural products in the world. If we had to choose between the complete elimination of, let us say, wheat, corn, or rice, or anything made by man, whether it be the incandescent lamp, the telephone, the radio or the aeroplane, there is no question which we would select to keep.

In the earlier stages of civilization plants naturally played a more important part in the lives of men. Wars were fought over spices, and the nation which could control the world supply of grain was the dominant one. It was the quest for plants, quite as much as for gold, that inspired many of the earlier navigators to sail unknown seas, and the valor and heroism of these seekers for the products of the vegetable kingdom has not been exceeded by any of our modern explorers.

With the great strides made in chemistry and physics and the discoveries and inventions based on these newer sciences, botany, together with the fundamental importance of the products of the laboratory of the living plant, has been somewhat over-shadowed if not forgotten.

It is proper therefore that a botanical garden should be the one to remind you that we are still very dependent upon the vegetable kingdom; that gold and iron, electricity and steam, are of little value without the myriads of things produced by plants. It is particularly fitting that to-day we should gather to celebrate what we believe to be the three-hundredth anniversary of the first recognized use of the bark of a tree that has played such an important part in the history of the world—a plant product that has brought more comfort to mankind than any number of the modern inventions of which we are so proud, one that because of its specific dominance over one insidious and widely spread disease, not to mention its other applications, has, indirectly at least, been the

means of creating wealth far beyond anything we can imagine. Where would we be to-day, what of the progress of art, of industry, of civilization itself, had it not been for the discovery three hundred years ago of the health-giving power of *Cinchona officinalis* and its allies? Nor should I fail to pay tribute to that nation long noted for its pioneering spirit which has through scientific investigation made possible the cultivation of this wild tree, thereby increasing many fold the natural source, that the nations of the earth might be healed. No country has been so active in the conservation of useful plants as Holland. In spite of almost unsurmountable handicaps as to soil and drainage and climate the Dutch have become the gardeners of Europe. In the East Indies they lead as growers and exporters of valuable tropical plant products, so that in proportion to population and area this little country has developed power from plants to a degree not attained by any other nation in the world.

Botanical or herb gardens had their origin in the growing of plants for the benefit of man. While of late the tendency in medicine has been away from drugs, it is interesting to recall that of the few real specifics we have for disease, practically all are more or less associated with plants. Even within the last few years there have been added to the pharmacopoeia such important products as those from the Indian chaulmoogra oil tree and the Chinese Ephedra. Indirectly the plant frequently takes a commanding position in the battle against the enemies of mankind. Only recently it has been announced that the blood-sucking tsetse fly was peculiarly sensitive to extracts of pyrethrum, as well as allied drugs like delphinine and veratrine. When these plant extracts, combined with cocoanut oil, are applied to a live animal, the fly which attacks by sight and not by smell, is so rapidly affected that no blood is drawn, and the insect is either picked up dead or dies shortly afterwards. But we need not multiply examples.

Perhaps the field of *materia medica* has been too much neglected of late. The old herb doctor practiced not only under the cloud of superstition but also in the light of experience. What appeared to be crass ignorance may have been accumulated knowledge. Could anything seem more absurd than the practice

of giving charred sponge for goitre, the custom for hundreds of years along the Mediterranean? Yet the marine sponge may run as high as four per cent iodine. And just now comes the news of the discovery of a preventive for goiter derived from certain plants. I need not refer to the modern use of the drug now known to be present in the glands of the frog skin, an ingredient which played so important and seemingly useless a part in the Chinese pharmacopoeia.

As Dr. Harvey Cushing wrote not long ago:

"An independent botany has emerged from the search in all corners of the earth for medicinal herbs that conformed to the therapeutic law of signatures; our medical schools no longer have their physick gardens, yet who knows what of value equal to digitalis may still be hidden in plants were there modern Witherings to look for them." (Science November 22, 1929. p. 488).

And so it is both a privilege and a pleasure for me, in the name of the Trustees of the Missouri Botanical Garden, to welcome you here on this occasion. May the program which has been arranged repay in some measure those of you who, coming from a distance, have honored us by your presence. May the event we are celebrating to-day, remind not only us, but the entire world, of the great debt we owe to plants in general and to Cinchona in particular.



THREE CENTURIES OF CINCHONA

LEO SUPPAN

Professor of Pharmacognosy, St. Louis College of Pharmacy

I. TRADITION

Among the unpublished papers of Joseph de Jussieu there exists a manuscript note, made in the course of his expedition in South America, and written in Latin, which is cited by Weddell.¹ In this note Jussieu purports to tell how the knowledge of the febrifuge properties of cinchona bark first came to the Spaniards. It is worth quoting in its entirety:

Certum est qui prius notitiam virtutis et efficaciae hujus arboris habuere, fuisse Indos vici *Malacatos*. His, cum, ob calidum simul ac humidum et inconstantiam temperamenti ac inclementiam, febribus intermittentibus maxime essent obnoxii, remedium tam importuni morti quaesivisse necessum fuit; et, cum, regnantibus Ingas fuerunt Indi botanices periti et virtutum herbarum indagatores acerrimi, facta variarum plantarum experientia, tandem kina-kina corticem ultimum ac fere unicum intermittentium febricum specificum remedium invenire. Nec alio nomine apud illos arbor nota quam ab effectu. Vocarunt *Yara-chucchu*, *Cava-chucchu*. *Yara* idem est ac arbor; *cava* idem est ac cortex; *chucchu*: horripilatio, frigus, febris horripilatio; quasi diceret arbor febrium intermittentium. *Ayac-cava* vocarunt quasi diceret corticem amarum.—Forte fortuna, tum unus ex societate Jesu iter habuerat per vicum *Malacatos*, is laborans febris intermittente. Misericordia commotus Indorum dux, *Cacique* vocant, cognito R. P. morbo: Sine paulum, inquit, et ad sanitatem perfectam te restituiam. Hoc dicto, exiit ad montem Indus, corticem dictum attulit et decoctum ipsius patri proponavit. Sanatus et ad perfectam sanitatem restitutus Jesuita, perquisivit quod genus medicamenti applicaverat Indus. Cognito cortice, hujus non exiguum quantitatem collexit Jesuita, et, ad patriam redux, eadem ac in Peruviana regione pollere expertus est, inde notus primo fuit cortex *Pulveris jesuitici* nomine; deinde *Pulveris cardinalitii*; et, cum simul inter varia fructuum et resinarum specimina, fructus arboris Quina-quina attulerat jesuita, fructum arboris fugandis febribus intermittentibus existimarunt; nec jesuita contradicere poterat, cum arborem nec viderat nec cognoverat; solummodo corticem attulerat; valeatque Quinaquina in febribus fugandis non exigua virtute.

As is usual in such cases, no date is given to this alleged event.

The belief expressed by Jussieu that the febrifuge qualities of cinchona were known to the Indians of South America long before the advent of the Spaniards was common to the earlier writers on the bark. Stories were even told of the manner in which the

¹ Weddell, H. A. *Histoire naturelle des quinquinas*. Paris, 1849, p. 15.

Indians became aware of its virtues. Thus, La Condamine tells us that the Indians, having observed that the South American lions, who were much afflicted with the tertian fevers prevalent in the regions where the cinchona trees grow, were cured by chewing the bark, tried it in their own cases, and found that it gave them relief.² Geoffroy says that an Indian was cured of an ague by drinking at a pool into which some cinchona trees had fallen. William Arrot, a Scotch surgeon who visited Peru in the early part of the eighteenth century, Ruiz and Pavon, Markham, and others, believed without question that the Indians knew the value of the remedy.

It would appear that these legends, for they were no other than such, were of European origin; for La Condamine himself states that when he attempted to obtain information regarding the matter in and about Loxa and Lima, none was forthcoming from the natives, not even the oldest of them.³ He appeared, indeed, to have founded his belief upon a statement of Antoine Bollus, a Genoese merchant who traded in South America and who is mentioned in a work of Sebastian Badus, published at Genoa in 1663, entitled 'Anastasis Corticis Peruviani, seu Chinae-Chinaee defensio.' "The natives," says La Condamine, "kept it secret from the Spaniards for many years. . . . They employed the bark by letting it lie in water for a day and then giving the patient the strained infusion to drink."

The most recent defender of this view was Mr. Henry S. Wellcome, who visited South America in 1878, spending some time in the principal cinchona districts, and presented an account of his travels in a paper read before the American Pharmaceutical Association in 1879. Referring to the alleged discovery of the medicinal virtues of cinchona by the Indians, he admits that it is still a matter of controversy. He believed, however, that the Indians did possess such knowledge and that they communicated it to their conquerors; but it was the policy of the *conquistadores* to arrogate to themselves the credit for the discovery and invention of all the useful things they found in the countries that they

² La Condamine, C. M. Sur l'arbre du quinquina. (Histoire de l'Academie Royale des Sciences, anno 1738). Paris, 1740. Reprinted in Monumenta Pharmaceutica. 1914, p. 7.

³ L. c. p. 13.

conquered, and thus it happened that, by the aid of the Spanish priests, whose ambition it was to destroy every relic of native civilization, the Indians were cheated out of their just claim to the discovery.⁴

However all this may be, it is a fact that between the discovery of Peru by the Spaniards in 1513 and up to the beginning of the seventeenth century, none of the writers who possessed first-hand information regarding the resources of the conquered country make any reference to the febrifuge bark. No mention is made of it in the lists of Indian remedies given by the Inca Garcilasso de la Vega and by Acosta; no specimens of *Cinchona* have been discovered in Inca tombs as have some of coca; and the stocks of the itinerant Indian physicians, whose *materia medica* was transmitted from father to son for many generations, contained no cinchona bark.⁵ Furthermore, the Indians themselves, after the Spaniards had learned the value of the bark, were not only ignorant of its medicinal properties, but absolutely refused to use it as a medicine when its value was pointed out to them. Humboldt, who rejected the Indian tradition *in toto*, called attention to the lack of any basis to support it. He declares:

It is not probable that the discovery of the medicinal properties of *Cinchona* is attributable to the primitive nations of America, when it is considered that they, like the Hindus, adhere with tenacity to their customs, their food and even their medicines and that the use of cinchona bark is entirely unknown to them at Loxa, Guancabamba, and for a distance around. In the deep and hot valleys of the mountains of Catamago, Rio Calvos, and Macara, agues are extremely common. But the natives there, as well as at Loxa, of whatever caste they be, would die rather than have recourse to *Cinchona* bark which, together with opiates, they place in the class of poisons inciting mortification. The Indians treat their fevers with lemonade, with the oleaginous rind of the small green wild lemon, with infusion of *Scoparia dulcis*, and with strong coffee. In Malacatos only, where many bark-peelers reside, are they beginning to put confidence in *Cinchona* bark. In Loxa is to be found no document to indicate the history of the discovery of *Cinchona*; an old tradition, however, is current to the effect that the Jesuits, at the felling of the tree, had distinguished, as was their custom, the different kinds of trees by chewing their barks and that on such occasions they had noticed the intense bitterness of the *Cinchona*. There being always medical practitioners among the missionaries, it is said that they had tried an infusion of *Cinchona* in the tertian ague, a complaint

⁴ Wellcome, H. S. Proc. Am. Pharm. Assoc. 1879, p. 830.

⁵ Markham, C. R. Peruvian bark, a popular account of the introduction of cinchona cultivation in British India. 1880, p. 6.

which is very common in that part of the country. This tradition offers less improbability than the assertions of European authors, among them Ruiz and Pavon, who ascribe the discovery to the Indians. The medicinal properties of Cinchona were also entirely unknown to the natives of the Kingdom of New Granada.*

Pöppig, too, writing in 1830, observed the same repugnance on the part of the natives to cinchona. In Huanuco, where the tertian ague was prevalent, he found that the Indians would not use the bark; they believed it to be heating and therefore unfit for use in fevers which, they considered, arose from an inflammatory condition of the blood. Spruce recorded similar facts in 1861, and added that the bark peelers could not be persuaded that the drug was wanted by the Europeans for any other purpose than dyeing, and that even at Guayaquil there was a universal dislike to the use of quinine. Markham also testifies to the fact that the wallets of the native doctors never contained cinchona bark. Ulloa, who visited South America in 1772, is also a witness to the repugnance of the Indians to the bark. La Condamine remarks sententiously: "*La quantité de Quinquina qui passe tous les ans en Europe, a persuadé dans tout le Perou qu'on s'en servoit en Europe pour les teintures.*"

II. INTRODUCTION OF THE BARK INTO EUROPE

Rejecting the Indian traditions, it is in the highest degree probable that the Jesuit missionaries were the first to discover the virtues of cinchona bark; but as to how and when this took place, we are without a shred of information. If a date suffices to accept an event as historical, at least provisionally, then the history of cinchona bark may be said to begin with the year 1630, when, as is recorded, Don Juan Lopez de Cannizares, Spanish Corregidor of Loxa, was cured by the bark of an intermittent fever. As an isolated fact, this would have an interest of its own; but it has an added significance from the circumstance that this same corregidor was instrumental in bringing the febrifuge to the notice of an exalted personage who, in turn, transmitted it to the physicians of Europe.

* von Humboldt, A. Gesellschaft naturforschender Freunde zu Berlin Magazin, 1807, I, p. 60.

† La Condamine, l. c. p. 11

The story of the recovery of the Countess of Chinchon from an intermittent fever by the use of cinchona bark has been told many times with a number of minor and unimportant variations; but all the accounts are consistent in the main features so that, although Humboldt relegated it to the limbo of fables, there is no sound reason for rejecting its validity:—In 1628 Don Luis Geronimo Fernandez de Cabrera, Bobadilla y Mendoza, fourth count of Chinchon, was appointed viceroy of Peru by the King of Spain, Peru at that time being the name given to the whole of the Spanish possessions in South America, and in January 1629 he, accompanied by his countess, Doña Ana, made his entry into Lima, the seat of the viceregal government. In 1638 the Countess was stricken by an intermittent fever which refused to yield to the remedies known at the time to the Spanish physicians. Hearing of this, the Corregidor of Loxa, mindful of his own cure several years previously, sent to his superior, the Viceroy, a quantity of cinchona bark with the assurance that it would drive away the Countess' fever. The Corregidor was thereupon summoned to Lima in order that he might in person instruct the Countess' physician, Dr. Juan de Vega, in the preparation and administration of the bark. Preliminary tests were made upon a number of patients, and these proving successful, the febrifuge was administered to the Countess with the happy result guaranteed by the Corregidor. The Countess was so delighted that she ordered—La Condamine quotes Badus as stating that it was at the solicitation of the city of Lima—a supply of the bark from Loxa, which, upon its arrival, she distributed, gratis, at the palace, to all who were in need of it, in consequence of which it became known as the *polvo de la Condesa*. After a few months she found this ministration to have become a task beyond her powers, and she transferred it to the Jesuits, who continued the work of charity. The bark now became popularly known as the *polvo de los Jesuitos* or *de los padres*. (Flückiger thinks that this name may have been given in memory of the Jesuit father cured of the fever as related by Jussieu.)

In 1640 the Count and Countess of Chinchon returned to Spain, and this year is supposed by many historians to mark the introduction of cinchona bark into Europe. But Badus, quoted

by Bergen, gives an extract from a letter of a Spanish physician, Dr. Joseph Villarobel, from which it appears that the bark was known in Spain as early as 1632, though no trial of it was made until 1639. Indeed, even at the time that Badus wrote, it was a mooted question whether the bark was introduced by the Countess or by the Jesuit fathers. If the early date assigned by Villarobel be correct, the bark was imported, but no trial, in the medical sense, of it was made until 1639, it is difficult to understand for what purpose it was imported in the first instance. According to Flückiger, the bark certainly appears to have been used in Alcala de Henares, near Madrid, in 1639.⁸ At any rate, in whatever year it may have first made its appearance in Europe, it certainly became rapidly and widely known not long after 1640, its dissemination and favorable reception being due mainly to the activity of the Jesuit Fathers, among whom the Cardinal de Lugo was the most prominent in zeal for the new remedy. It was at the instigation of this benefactor of the human race that the nature and the medicinal properties of the bark were investigated by order of Pope Innocent the Tenth.

Juan de Lugo was born at Madrid in 1583, entered the Society of Jesus in 1603, and was made a cardinal in 1643. He died at Rome in 1660. In his capacity of Attorney-General of his order he had, it appears, the superintendence of the Jesuit pharmacy in Rome, from which the drug was for a time distributed gratis to the poor, though the Cardinal also gave it away in his palace. It was from him that the remedy became known as *pulvis eminentissimi cardinalis de Lugo* or *pulvis cardinalis*, although it was also called *pulvis patrum*, in reference to the Jesuits. In 1649 the Cardinal passed through Paris where the Dauphin, afterward Louis the Fourteenth, lay ill of a fever. De Lugo recommended the bark to Cardinal Mazarin as the proper remedy for the Dauphin's illness. A supply was furnished, and the prince recovered.⁹

On the occasion of the return of the Count of Chinchon to

⁸ Flückiger, F. A. and D. Hanbury. *Pharmacographia: A history of the principal drugs of vegetable origin met with in Great Britain and India.* 2nd edition. London, 1879, p. 343.

⁹ Sprengel, K. *Versuch einer pragmatischen Geschichte der Arzneykunde.* Halle, 1827, IV, p. 519.

Spain in 1640, Juan de Vega, who had attended the Countess in her illness at Lima, brought a supply of the bark with him, and in 1649 the Jesuits received a quantity from their Provincial in America. From the evidence at hand it appears that the year 1649 marks the date at which the bark first attracted the attention of physicians throughout Europe. The interest aroused was in a great measure due to the cure of the Dauphin, and to the large supply that came from Peru in the same year that a general meeting of the Jesuit order was held in Rome, upon which occasion the drug was distributed far and wide through the instrumentality of the Jesuit fathers who returned to their homes after the meeting. According to Chifflet, physician to the Archduke Leopold William of Austria, Viceroy of the Netherlands, the bark was brought from Italy to Belgium, but large quantities were also imported into that country directly by Michel Belga who had resided several years at Lima.¹⁰ In Brussels and Antwerp the remedy was known as *pulvis Jesuiticus*; but it was more commonly called *pulvis Peruanus* or *Peruvianum febrifugum*. Roland Sturm, a physician of Louvain, wrote that in 1658 he saw twenty doses sent to Paris from Rome, which were sold for sixty florins; he also gives a copy of a handbill issued in 1651 which the apothecaries of Rome distributed with the powder sold by them, containing information as to the method to be followed for administering the remedy. The text of this document is as follows:

Modo di adoprare la Corteccia chiamata della Febre:—Questa Corteccia si porta dal Regno di Peru, e si chiama China, o vero China della febre, laquale si adopra per la febre quartana e terzana, che venga con freddo; s'adopra in questo modo, cive: Si ne piglia dramme due, e si pista fina con passarla per setaccio, e tre ore prima incirca che debbe venir la febre, si mette in infusione in un bchiere di vino bianco gagliardissimo, e quando il freddo comincia a venire o si sente qualche minimo principio, si prende tutta la pressa preparata, e si mette il patiento in letto.

Avertasi, si potrà dare della corteccia nel modo sudetto nella febre terzana, quando quella sia fermata in stato di molti giorni.

L'esperienza continua ha liberati quasi tutti quelli che l'hanno presa, purgato prima bene il corpo, e per quattro giorni dopo non piglia nuina sorte di medicamento, ma avertiasi di non darle se con licenza degli Sgr, medici, acciò giudicano se sia in tempo proposito di pigliarla.¹¹

¹⁰ Sprengel, *l. c.* p. 520; Flückiger, *The cinchona barks pharmacognostically considered*. [Translated by Frederick B. Power. Philadelphia, 1884, p. 84.]

¹¹ Flückiger and Hanbury, *l. c.* p. 343.

It was in 1654 or 1655 that cinchona reached England, and it was probably already extensively used in 1658, in which year there was an epidemic of intermittent fever in England, for George Baker mentions an advertisement of that date in which the medicine known as *Jesuit's powder* is offered for sale; this powder is stated to have been brought from Antwerp by a merchant. At about the same time, Brady, professor of physic at Cambridge, was prescribing the bark. Dr. Thomas Willis, a physician famous in his day, has also left a record of its use at that time. Willis himself does not appear to have had confidence in it up to 1659, but in the following year he writes of cinchona as being extensively used, although he is cautious in speaking as to its efficacy. In 1662 he expresses the opinion that the value of the bark is to be determined solely by the results of its use, and not by any theories regarding its chemical or other properties.¹²

Physicians, as a class, were still somewhat in the dark as to the proper time for administering the bark as well as the most efficacious mode of presenting it to the patient. The clearing up of these doubtful points must be placed to the credit of that ambiguous individual who is known to us by the name of Robert Talbor, but whose family appellation was really Tabor. Historians of medicine, if they deign to mention him at all, present him in the character of a consummate quack. That Talbor had many characteristics of the charlatan and was skillful in putting them to practical use cannot be denied. The methods he employed in diffusing the use of cinchona bark leave no room for doubt:—he kept the composition of his preparations of the bark a secret; in his advertisements he even went so far as to point inuendos against the *Jesuit's powder* in order to throw the purchasers of his medicine off the track; and yet, be it said to his credit, he made considerable improvements in the method of administration and in determining the appropriate time and the doses to be observed in the course of treatment.

Robert Talbor, or Tabor, was born in 1642 and died in 1681. His birthplace was Cambridge, and he appears to have gone through the course in physic at the university there, for Sprengel states that the archives of the University record that in 1663

¹² Sprengel, *l. c.* p. 522; Flückiger and Hanbury, *l. c.* p. 344.

Robert Tabor, son of John Tabor, was elected a subsizar of St. John's college for five years, which appears to dispose of the charge frequently made against him of being an irregular practitioner. It has been said that he was at one time assistant to a Cambridge apothecary named Dear, and that it was while serving in this capacity that he received from Dr. Nott, a member of the University, certain hints as to the best methods of employing cinchona.¹³ In fact Talbor himself, in his 'Pyrotologia,' published in 1672, admits that certain hints which he had received from Dr. Nott were the cause of his own subsequent good fortune. That Talbor, whatever his faults might be, was possessed of the scientific spirit, must be granted him. Before launching his ideas, or Dr. Nott's ideas if you choose, he put them to the test. He settled on the coast of Essex where he carried on a series of experiments with his preparations. So successful were the results that his name became known and he was frequently called to London in his professional capacity.¹⁴ He finally settled in the capital in 1671, where in the following year he published his 'Pyrotologia, or a Rational Account of the Cause and Cure of Agues.' In this pamphlet, which is a kind of manifesto, he proclaims that he effects the cure of tertian and quartan agues by means of a secret remedy consisting of four ingredients, two of which are native to England, the other two coming from abroad. He refers disingenuously to the *Jesuit's powder*, declaring that it must be used with the greatest caution, admitting it to be an excellent remedy when employed with understanding but declaring that its use was apt to be attended with inconveniences and dangers leading even to convulsions, as he himself could testify. As this declaration stands, it expresses nothing but the truth; but it leads to the impression, as he probably designed, that the Peruvian bark was absent from his preparation. As was to be expected, the other physicians, and especially organized medicine, were roused, and it is stated that Talbor was obliged to appeal to the protection of Government against the persecution of the College of Physicians. In this affair Talbor took the tricks and the honors too, for he was appointed physician to Charles the Second in 1678 and at the same time knighted.

¹³ Sprengel, *l. c.* p. 528.

¹⁴ *Ibid.* p. 528.

Talbor's reputation extended beyond the bounds of his own country. In 1679 he went to Paris, where he employed his remedy with such success that he was recommended to the Court, where the health of the Dauphin was entrusted to his care. Here again fortune smiled upon him. Louis XIV purchased his secret for 2000 louis d'or and at the same time granted him a life pension of 2000 francs—all to the intense disgust of the medical fraternity. When Talbor died, in 1681, Louis ordered the publication of his method of curing the tertian and quartan ague. The execution of the task was undertaken by Nicolas de Blegny, surgeon to the King. The title of Blegny's pamphlet is 'Le Remede anglais, pour la guérison des fièvres, publié par ordre du Roy, avec les observations de M. le premier Médecin de sa Majesté sur la composition, les vertus et l'usage de ce remède,' par Nicolas de Blegny, chirurgien ordinaire du corps de Monsieur et Directeur de l'Academie des nouvelles découvertes de Médecine, Paris 1682. It was now discovered that the famous remedy was nothing but the well-known *Jesuit's powder*, sometimes combined with opium, and associated with other substances to disguise its taste—in short a "proprietary," in modern parlance. The discovery did not, however, bring the preparation into discredit: De Blegny's memoir was at once translated into English under the title 'The English Remedy: or Talbor's Wonderful Secret for the Curing of Agues and Fevers—Sold by the Author, Sir Robert Talbor, to the Most Christian King, and Since his Death ordered by his Majesty to be published in French, for the Benefit of his Subjects.' This was published in London in 1682. Blegny was a man of Talbor's own type. Soon after Talbor's arrival in Paris, Blegny put out a remedy of his own for intermittent fevers composed, Sprengel says, of cinchona, opium and "salt of vipers," which he proceeded to exploit in the most shameless fashion. He was apothecary as well as physician, and appears to have trod devious paths in both professions, for we read of him as being a "swindler" and of having been consigned to the Bastille in 1686, for what offense is not stated.

Whatever be Talbor's demerits, it cannot be denied that he made far-reaching improvements in the preparation and administration of the bark, and the publication of his secret gave a

powerful impetus to its popularity. It even inspired the pen of a poet: in 1682, La Fontaine, at the solicitation of the Duchess of Bouillon, who had experienced the beneficence of the *Jesuit's powder*, composed a poem in two cantos in celebration of the virtues of the Peruvian drug, which was published, together with other pieces, under the title 'Poème de Quinquina et autres ouvrages en vers.' Further, Madame de Genlis wrote a short tale on the cure of the Countess of Chinchon, entitled 'Zuma'; her story was translated into Spanish in 1827 with the title 'Zuma, ó el Descubrimiento de la Quina, Novelda Peruana.'¹⁵ It need hardly be said that both science and history suffered gross maltreatment at the hands of La Fontaine and Madame de Genlis.

As has been remarked, Belgian officials had a share in the distribution of the bark. One of the most active was Chifflet, physician to the archduke Leopold William, who published in Brussels, 1651 or 1653, a pamphlet bearing the title 'Pulvis febrifugus Orbis Americani ventilatus,' which had considerable influence in the medical world of Europe. The author declared the drug one of the marvels of the age but was somewhat lukewarm in its commendation. In Germany the bark was called *China China*; it occurs in the pharmaceutical tariffs of Leipzig and Frankfurt for 1669, the latter fixing the price of one quint ($\frac{1}{8}$ ounce) at 50 Kreutzer (about 38 cents), the same quantity of opium being quoted at four Kreutzers, camphor at two, and balsam of Peru at eight.¹⁶ In 1664 it was declared a dutiable product at Lyons. It first appeared in the London Pharmacopoeia in 1677 under the name of *Cortex Peruviana*; and it is recorded that in 1692 priests of the Jesuit order stationed in China were already in possession of quantities of it and cured the emperor K'ang Hsi of a dangerous fever.

The diffusion of the bark, however, did not proceed without opposition. Various interests united in a violent cry against it. There was, first of all, the religious motive. The Protestants scented a Jesuit plot; the bark was an insidious poison which the Jesuits had brought to Europe for the purpose of exterminating all those who had thrown off their allegiance to Rome. This, of

¹⁵ Markham, *l. c.* p. 10.

¹⁶ Flückiger, *Cinchona barks*, p. 85.

course, appealed to the ignorant, and as a consequence the use of the bark was confined almost exclusively in Protestant countries, to the convents and other Roman Catholic religious establishments.¹⁷ This silly prejudice, however, soon died out. Then there was the army composed of the Galenists and other medical dogmatists who, finding that the nature of the bark did not fit into their ancient theories, would have none of it. Soon a violent controversy arose which lasted many years, in which men of undoubted attainments and others of less note were arrayed on both sides. Division soon took place among the Spanish physicians. In 1642 Pedro Barba, physician to the Cardinal Prince Ferdinand, Governor of Belgium and brother of Philip IV of Spain, wrote in defense of the bark. Not long after, a certain Joseph Colmenero launched a violent diatribe against it, based upon medico-philosophical grounds, which was answered by Gonzalo Tomas Hernandez. Hernandez justified the use of the bark by the results of experience.

Not all the opponents of the new febrifuge were Galenists, nor did all the Galenists appear in the ranks of the opposition, and a number of these, practising in Rome, accepted the remedy without question. Conflicts of this kind accompany every innovation, and, in the case of cinchona, the controversy would have taken the regular course, school quarrelling with school, had not an event occurred which shook the faith of even the most impartial physicians and threatened to discredit the bark in the eyes of all practitioners:—Leopold William of Austria, Governor General of the Netherlands, suffered severely from a double quartan ague, for which cinchona bark, brought to Brussels by Michel Belga was prescribed with success; but a relapse took place, and the Governor General refused to take more of the bark, whereupon he died.¹⁸ Chifflet, his physician, published the work already mentioned, in which he gave an account of the prince's illness and, while not directly attacking the bark, wrote of it in so lukewarm a style that the pamphlet was eagerly seized as a weapon by the opposition.¹⁹ The very man who had prescribed the bark was

¹⁷ Sprengel, *l. c.* p. 519.

¹⁸ *Ibid.* p. 520.

¹⁹ Goebel, F., und G. Kunze. *Pharmazeutische Waarenkunde*, I, Eisenach, 1827–29, p. 101.

disappointed in it, it was urged, and practically admitted its worthlessness! The fact is that Chifflet's grounds of doubt were of an altogether theoretical character. A reply was called forth from Honoratius Faber, who wrote under the name of Antimius Conygius; this pamphlet, which was afterward appended to Chifflet's work, gives a chemical analysis of the bark—so far as chemical analyses went in those days—and he based his contention in favor of the bark upon the action of its volatile constituents. Faber had an ally in Pedro Castilli, who advocated the bark in his '*De effervescentia et mutatione colorum in mixtura liquorum chymicorum*,' published in 1654. To these two works came a reply from Vopiscus Plempius who, under the name of Melippus Protinus, issued a pamphlet bearing the title '*Antimius Conygius, pulveris peruviani defensor*' and published at Louvain in 1655. Plempius sought to prove that far from being efficacious in intermittent fevers, the bark worked the other way, converting them into permanent ones. He ventured to assert that not only had no single cure been effected by the bark in Brussels but that its use had invariably been followed by bad results, especially in Italy. He goes so far as to speak of a letter written by the King of Spain, emphatically condemning the bark; this letter was probably evolved out of Plempius' imagination.²⁰

One of the most learned and impartial defenders of cinchona was Roland Sturm, a physician of Delft, whose '*Febrifugi peruviani vindiciarum, Pars prior*,' appeared in Antwerp in 1659.²¹ He submits the opposing arguments of Chifflet and Plempius to a critical examination. He is severe with those physicians who attack a valuable remedy with a prejudiced mind and condemns the ignorance and stupidity of those who have the audacity to decry as worthless or even dangerous a remedy with which they have had no experience. He rejects all fanciful theories and appeals to experience which had demonstrated amply the value of cinchona; and he regrets that the bigotry of certain physicians of dogmatic temperament had well nigh brought the bark into universal discredit.²²

²⁰ Sprengel, *l. c.* p. 522.

²¹ Goebel & Kunze, *l. c.* p. 101.

²² Sprengel, *l. c.* p. 523.

In Italy, also, the battle raged fiercely. In 1661 the bark was prescribed for Cardinal Doughi, who was suffering from a tertian fever. When they were apprised of this, two Galenists of Milan, Cristoforo Paravicini and Rochus Casati, launched their denunciations against this example of heresy. Paravicini was the more moderate of the two; he was frank to admit that the bark might be of some use in ordinary quartan fevers, but denied its value in the typhoid kind, which is the one that seems to have seized upon the Cardinal. Casati, however, was a Galenist of the hide-bound kind, and indulged in indiscriminate denunciation.

Curiously enough, attempts were made by some men of a compromising spirit to fit cinchona into the Galenic system. The most curious was that of Gaudentius Brunaculus, a Roman physician, who appeared as champion of the bark against its detractors. He bolstered up his arguments with principles drawn from the scholastic philosophy as well as from the therapeutics of Galen. Nevertheless, he displays some glimmer of reason even in the midst of his metaphysical fooleries, for at times he stresses the value of experience in matters medical. He cites as evidence in favor of the bark the results obtained with it in the Archepiscopal Hospital of Spiritu Santo in Rome. Indeed, he himself had been cured by the bark of a double tertian ague which had afflicted him for a month.²²

Sebastian Badus, of Genoa, was a defender of the bark in his 'Anastasis Corticis Peruviani' already mentioned. He had the advantage of speaking from direct experience, for he had assisted Cardinal de Lugo in distributing the febrifuge in Rome. Badus demonstrated the futility of theory in judging of the value of the bark. His special design in writing the 'Anastasis' was to expose the fallacies of Chifflet and Plempius.

A number of physicians of open mind, who at first opposed the use of cinchona or at least doubted its efficacy, were later converted to the other side. Among these was the famous English physician, Thomas Wallis, an adherent of the iatro-chemical school, and, naturally, disposed to advocate the treatment of disease on the basis of chemical affinities. In 1659 he discoursed in a rather vague fashion of a certain powder which, he says, came

²² Sprengel, l. c. p. 525.

from India, and was said to be of value in the treatment of intermittent fever—from which we may conclude that his knowledge of the bark was meagre ('*Diatribae duae de fermentatione et febris*'). In a supplement to his work, published a year later, he states that the fever bark was being extensively used in intermittent fevers, but his judgement of the remedy was not altogether favorable; he granted, indeed, that it might check the "fermentation" of the fever but could not cure it permanently. But in the third edition, which appeared in 1662, he frankly confesses that experience had proved its virtue and that chemical theories alone do not furnish a criterium as to how a given remedy will act.²⁴ Dr. Morton, also an English physician of distinction, was another who opposed the bark in the beginning and later retracted his earlier expressions—a circumstance that did much to restore the bark to favor. Other adherents of the iatro-chemical and Galenic schools who became converts to the cause of the bark were Jacques Minot, Casper Bravo de Sobremonte, Ramirez, a professor at Valladolid and physician to the Spanish Court, and Andriolli.

One of the strongest supporters of the anti-cinchonists was Bernardino Ramazzini. Although he wrote rather against the unintelligent use of the drug than the drug in general, he, unfortunately, advanced certain objections of a philosophical nature against it that were eagerly seized upon by the Galenists in their favor. He was criticized by the Venetian, Bernardo Zendrini, who, although he was hampered by Galenist prejudices, is regarded by Sprengel as the ablest of the older expounders of the pharmacology of cinchona. His work is of some historical importance in that it throws light upon one of the probable causes of the loss of faith in the bark on the part of many physicians. He states that the cinchona first introduced into Europe was far more effective than that which could be obtained in his time, for of the former, smaller doses were far more effective than large doses of the more recent barks.²⁵

The most violent enemy of cinchona appeared after the fury of the contest had in a measure died out and the bark had become

²⁴ Sprengel, l. c. p. 524.

²⁵ *Ibid.* p. 539.

an established article of the *materia medica*. This was Gideon Harvey, whose 'Ars curandi morbos expectatione' appeared in London in 1689. This work is a scurrilous diatribe against physicians in general. The idiom, a barbarous Latin, admirably fits the matter. Harvey divides physicians into six classes: the Iron-Doctors, the Ass-Doctors, the Jesuit-Doctors, the Water-Doctors, the Butcher-Doctors, and the Teeth-Doctors. The Jesuit-Doctors are, of course, those who prescribe cinchona which, in the opinion of Harvey, is an utterly worthless drug. It is curious that this work was recommended for the perusal of an intelligent public by no less a person than the phlogistinish Stahl. It probably caused more amusement than disgust, for the polemics of those days were not of the kid-glove variety. It certainly did nothing to bring fresh discredit upon cinchona bark.²⁶

While bigotry, religious, philosophical, and medical, and the appeal to conflicting theories played a role in the great cinchona controversy of the seventeenth century, there can be no doubt that other circumstances of a more positive nature were contributory. Of serious import was the lack of knowledge on the part of many physicians of the proper time for administration of the bark and the method of preparing the drug so as to insure its full effect. Dr. Sydenham, for example, tells us that in his time the bark had fallen into discredit in England for the reason that physicians did not know how to graduate the doses properly or what was the proper time to give it. He asserts that several people had actually died after taking it. This was a defect that experience only could remedy. It was here that Talbor achieved much good. His discoveries, when they became public property, were a revelation to physicians and did much to place the bark upon a firm footing. Another cause must be sought in the substitution of other barks, either through ignorance or wilful sophistication or the use of inferior barks for good ones. There was no art of analysis in those days that enabled dealers to distinguish between the different varieties, nor was there any scientific knowledge of the trees from which the bark was obtained. We have seen Zandrini's statement regarding the inferiority of the more recently imported barks to the older. Indeed,

²⁶ Sprengel, l. c. p. 541.

Cardinal Lugo already complained of sophistication, declaring that all kinds of astringent barks were being exported from South America to Italy, some of which had been made bitter with aloes and sold to the unwary as the true Jesuit's bark. Sturm, in 1661, complained that good bark had become so scarce in his time that it could be afforded by the powerful and wealthy classes only and that princes presented it to one another as a gift of almost priceless value. He declared his failure to understand how the bark could be so plentiful about Loxa when it was so scarce and dear in Europe. He himself had for five years dispensed the Jesuit's powder from a store which a friend had presented to him, and when this was exhausted he was unable to secure a new supply.

That the adulteration of cinchona bark assumed huge dimensions in the country of its source is vouched for by La Condamine, who gives a circumstantial account of the tricks of trade practised both at the sources of production and at the places of export, and he points out the inevitable results that follow such practices. The demand for the bark came from Europe in so short a time, he tells us, that it was soon in advance of the supply; the bark became scarce at Loxa, and the collectors resorted to adulteration. As a consequence, the demand fell off to such an extent that bark which had at one time fetched as much as four to five piastres the pound at Panama, and twelve at Sevilla, had fallen in price to half a piastre. In 1690, he says, several thousand pounds of bark were stored at Piura and at Payta, the port nearest to Loxa, nobody caring to ship it. It was this stagnation in the bark trade that led to the ruin of the town of Loxa. Of the adulterants employed La Condamine mentions the bark of a tree called the *Alizier*, lighter in color on the outside and a deeper red internally than the genuine Loxa bark. The most popular adulterant, however, he avers, was the bark of a *Cucharilla*, which resembled the cinchona bark very closely in its outward characteristics, although the tree from which it was obtained was very different from that furnishing the fever bark. In spite of the similarity of the barks, an expert could discriminate between them, and in order to detect the sophistication it was customary to inspect each bark carefully, a procedure which La Condamine

himself witnessed at Payta. Unfortunately purchasers were not as a rule experts and deception was common.²⁷

Flückiger suggests that it is conceivable that barks other than cinchona possessing a bitter taste might have been mistaken for cinchona bark, citing in point *cascarilla* bark, derived from *Croton Eluteria*, a small tree of the Euphorbiaceae, growing in the West Indies, which is bitter and at the same time aromatic, and which found its way into Germany at the close of the seventeenth century under the name of *China nova* but soon passed into oblivion.²⁸ It is odd that at the beginning of the nineteenth century the same name, *cascarilla*, should have been bestowed upon an entirely different bark, *Cascarilla magnifolia*. We shall meet in the sequel with an unfortunate application of the name in the distinction made between "true" and "false" cinchonas by Weddell. Considering this example, it may be indeed supposed, thought Flückiger, that still other barks were confused with cinchona by the collectors or deliberately used for purposes of sophistication, to appear in Europe under the name of Peruvian Bark.

Sprengel cites one more cause for the hostility that for a long time prevailed against cinchona bark, the famous Dr. Morton being his authority. Morton declared that it had been the practice of physicians to prolong the course of intermittent fevers by the administration of all kinds of debilitating substances, to their own profit and that of the apothecaries. When, therefore, a remedy appeared which could be administered in comparatively small doses and checked the fever in a short time, the gentlemen of the two healing fraternities found their income threatened with curtailment. They therefore organized a boycott against the new drug, which in a short time assumed the dimensions of an international conspiracy! *Se non è vero, è ben trovato*.

III. THE QUEST OF THE FEVER BARK TREE

Fully a century elapsed from the time of the introduction of the fever bark into Europe to the description of the tree; and, curiously enough, the first published account came from a man

²⁷ La Condamine, l. c. p. 9.

²⁸ Flückiger, *Cinchona Barka*, p. 85.

who was not a professed botanist but an astronomer. This man was La Condamine. Charles Marie de La Condamine was a type of the French *savant* of the eighteenth century, alert, keen, interested in all the scientific knowledge of the day, his command of which he turned to account in various directions. He was born in Paris in 1701 and was trained for the military profession but soon turned his attention to science and geographical explorations. In 1731 he took part in a scientific expedition to the Levant, after which he became a member with Louis Godin and Pierre Bouguer of the expedition sent to Peru in 1735 to determine the length of a degree of the meridian in the neighborhood of the equator, near Quito, for the purpose of obtaining data for determining the form of the earth. La Condamine quarrelled with his associates and finally parted from them, going to Quito and proceeding thence to Cayenne by way of the Amazon. He was the first to make a scientific exploration of that river. The botanist Joseph de Jussieu accompanied the Godin-Bouguer expedition for the purpose of making such botanical observations as might be afforded in the course of the company's stay in South America. La Condamine, being under the necessity of going from Quito to Lima on affairs of business, and the rainy season suspending the astronomical observations, left Quito, January 18, 1737, provided with notes by Jussieu concerning certain points regarding the natural history of the cinchona tree, and was requested by that botanist to note such observations as he might be able to make. Having two roads at his disposal, one by Guayaquil, the other by Cuenca, he chose the latter although the more circuitous and difficult, in order that he might pass by Loxa. On February 14 he observed one of the cinchona trees on the mountain of Cajanuma, about two and a half leagues from Loxa.²⁹ It was from this place, he says, that was derived the bark which was first sent to Europe. The Cajanuma bark was the most celebrated, and only fifteen years before La Condamine's arrival it was still the practice of the bark merchants to demand an affidavit certifying that the bark they purchased came from Cajanuma. La Condamine spent the night on the mountain in the hut of a bark collector who had chosen his domicile at this spot in order to be

²⁹ La Condamine, *l. c.* p. 2.

near the source of supply. On the road, both in going and returning, the astronomer had the opportunity of examining several of the trees at his leisure, and he sketched on the spot a branch with leaves, the flowers and the seeds, which accompanied the memoir which he sent to the Royal Academy of Science at Paris and which was published in the journal of that body in 1740.³⁰

La Condamine's memoir gives many interesting details regarding the kinds of bark which found their market at Loxa. In general, he says, three kinds are distinguished in the country, although some experts would recognize four. The three generally recognized are the white, the yellow, and the red. He was told that these differed only in the febrifuge qualities, the white possessing scarcely any, while the red was the most potent. There was no botanical difference in the trees from which the yellow and red barks were derived; it was only upon applying the knife to the bark that they could be distinguished, the yellow being lighter in color and softer in texture than the red. Both trees grew together in the same locality and the bark was stripped from both indifferently, the respective colors toning down to the same hue upon drying. Both barks were of the same brown color on the exterior, which is the characteristic accepted as a mark of a bark of good quality. The Spanish merchants further demanded that the exterior be rough, traversed by fissures and fracture readily.³¹

As for the tree yielding the white bark, his host assured him that the leaves were more rounded and less smooth than those of the other two. Also, its flower approached nearer to white, its seed was thicker, and the bark whitish on the exterior. The tree grew at a greater elevation and was never found mingled with the red and yellow, which preferred situations lower down on the slopes, in ravines and gorges and, in general, in regions densely wooded. La Condamine thinks that this variation in the white from the red and yellow varieties may be due to the place of its growth and to the greater degree of cold to which it is exposed. The time that La Condamine spent at Loxa being short, prevented his studying the subject in greater detail; moreover a minute

³⁰ La Condamine, *l. c.* p. 2.

³¹ *Ibid.*, p. 3.

examination would have demanded the exact knowledge of a botanist, the possession of which he modestly disclaimed. He adds, however, some details of general interest and importance regarding the habit of the cinchonas; for example, that the trees never grow on the plains; that the trees grow straight upward and to such a height that their summits rise far above those of the neighboring trees; moreover, they never occur in masses but isolated from one another and always surrounded by trees of other species. When allowed to attain their prime they become very large, the trunk attaining to the thickness of a man's body, the mean diameter being eight to ten inches; it was rare, in his time, however, to find many that had attained their full maturity, for the large ones from which the first bark had been stripped were dead. It had been found by experience that many of the small ones also died after having been stripped of their bark, but the greater number survived the operation. The great demand for the bark had resulted in nearly all the Loxa and Cajanuma trees being destroyed, except the youngest. The stripping is effected by means of an ordinary knife, which the stripper holds with both hands, driving it into the bark as high as he can reach and drawing it downward. La Condamine tells us that in the beginning the large, thick barks were preferred by the dealers but that later the thin, quilled pieces were most in demand. The reason for this, La Condamine was assured by the director of the English South Pacific Company, was that chemical experiments and medical experience had shown that the thinner barks were the most effective, and that the greater ease with which they could be dried and thus preserved against injury from moisture probably also contributed. The stripping of the tree is carried on at all times except during the rainy season. It was essential that the stripped bark should be exposed to the sun for some time to ensure thorough drying, as the packing of moist bark was sure to lead to its deterioration.

The precise species which La Condamine found and described became a subject of discussion among botanists of a later time. His description is somewhat general and his drawings, as Humboldt declared, are lacking in precision. But as his description is the first published, it is of historical interest to give it in his own words:—

Les feuilles sont portées sur une queue d'environ demi-pouce de longueur, elles sont lisses & d'un beau verd, plus foncé en leur partie supérieure & plus clair en-dessous, leur contour est uni & en forme de fer de lance, arrondi par le bas & se terminant en pointe: elles ont dans leur mesure moyenne un pouce & demi ou deux pouces de large, sur deux & demi ou trois pouces de long; elles sont traversées dans leur longueur, d'une côte arrondie par-dessous, et d'un rouge foncé & brillant, sur-tout dans la moitié voisine de la queue; cette couleur se communique souvent à la feuille entière dans sa maturité: les principales nervures sont alternes & parallèles à trois ou quatre lignes d'intervalle les unes des autres, elles forment avec la côte du milieu, des angles plus aigus que le demi-droit, & se terminent en s'arrondissant parallèlement au bord de la feuille. Quelques gens du pays prétendent que la feuille de l'excellent *Quinquina* de la meilleure espèce, est moins lisse et même un peu cotonneuse, je n'en ai point vu de telles.

Chaque rameau du sommet de l'arbre finit par un ou plusieurs bouquets de fleurs, qui ressemblent, avant que d'être écloses, par leur figure & leur couleur bleu-cendré, à celles de la Lavande; les boutons en s'ouvrant changent de couleur; le pédicule commun qui soutient un des bouquets, naît aux aisselles des feuilles et se divise en plusieurs pédicules plus petits, lesquels se terminent chacun par un calice découpé en cinq parties, & chargé d'une fleur de la même grandeur & de la même forme à peu-près que la fleur de la Jacinte; c'est un tuyau long de sept à neuf lignes, évasé en rosette taillée ordinairement en cinq & quelquefois en six quartiers; ceux-ci sont intérieurement d'un beau rouge de carmin vif & foncé au milieu et plus pâle vers les bords, et leur contour se termine par un liseré blanc en dents de scie, qu'on n'apperçoit qu'en y regardant de près; du fond du tuyau sort un pistille blanc chargé d'une tête verte & oblongue, qui s'élève au niveau des quartiers, & est entouré de cinq étamines qui soutiennent des sommets d'un jaune pâle, & demeurent cachées au-dedans, ce tuyau est par-dehors d'un rouge sale & couvert d'un duvet blancheâtre.

La fleur étant passée, le calice se renfle dans son milieu en forme d'olive, il grossit et se change en un fruit à deux loges, il devient plus court et plus rond en se séchant, & s'ouvre enfin de bas en haut en deux demi-coques séparées par une cloison & doublées d'une pellicule jaunâtre, lisse et mince, d'où il s'échappe presque aussitôt des semences rousseâtres applaties & comme feuilletées, dont plusieurs n'ont pas demi-ligne de diamètre, très-minces vers les bords & plus épaisses vers le milieu, qui est d'une couleur plus foncée et contient la plantule dans son épaisseur entre deux pellicules; ces semences qui m'ont paru ressembler en petit à celles de l'Orme, sont attachées et disposées en manière d'écaille, sur un placenta oblong & aigu par ses deux extrémités; ce placenta tient de chaque côté à la cloison mitoyenne, il a la forme à peu-près d'un grain d'avoine, mais plus long et plus mince, aplati, avec une cannelure selon sa longueur du côté qui joint la cloison, & rond avec quelques aspérités du côté opposé.

Il est fort difficile de saisir ces semences sur l'arbre même dans une parfaite maturité, en meurissant elles se séchent, et l'agitation du vent les fait tomber; en sorte qu'on ne trouve jamais sur la branche, que le fruit noué, mais encore vert aussi-tôt après la chute de la fleur, ou des capsules sèches & vuides.

On peut aisément reconnoître par cette description, combien ont été mal informés les premiers Auteurs qui ont écrit sur le *Quinquina*, & en particulier

*Sebastien Badus, Médecin Génois, dans son Traité intitulé Anastasis Corticis Peruviani seu Chinae Chinae defensio.*³²

La Condamine states that new cinchona trees were being discovered every day, not only on the mountain of Cajanuma but in places more distant from Loxa. He cites those found at Ayavaca, about thirty leagues southwest of Loxa, the bark of this tree being in high repute. Cinchona trees had also been discovered in the neighborhood of Rio Bamba, about forty leagues north of Loxa; near Cuenca, a degree of latitude farther north than Loxa, and a little farther east; and in the mountains of Jaen, fifty or sixty miles to the southeast. Considerable of the Jaen bark, which was said to be of the white kind mentioned, had passed into Europe; but, either because it was medicinally less active or because there was a prejudice against it, it had a bad name at Panama, and any bark that was known to have come from Jaen found no sale.³³

In 1743 La Condamine visited Loxa, whence he travelled to the Amazon River; it was on this occasion that he undertook the ill-starred experiment of transporting living young cinchona trees to Europe. He was successful in preserving them on a laborious voyage of eight months, but when his boat was not far from Cape Orange, near Pará, a huge wave swept over it, and the precious trees went by the board.

Two years after the publication of La Condamine's paper by the Royal Society of Sciences, Linnaeus established the genus *Cinchona* in the second edition of his 'Genera Plantarum.' It is ever to be regretted that he spelled the name of the genus as we now have it, instead of *Chinchona*, the more so because he desired to honor the memory of the Countess of Chinchon by giving her name to the new genus. Many years later Mr. Clements R. Markham attempted to induce botanists to adopt the correct spelling, and invariably used it himself in his writings, as did also Mr. John Eliot Howard; but the International Botanical Congress which met in London in 1866 and to which Mr. Markham's proposal was submitted, voted to retain the Linnaean spelling, and so it has remained to the present day.³⁴ In the first edition of the 'Species

³² La Condamine, *l. c.* p. 7

³³ *Ibid.* p. 10.

³⁴ Markham, *l. c.* p. 13.

Plantarum,' published in 1753, and in the second, which appeared in 1759, Linnaeus named the Loxa plant *Cinchona officinalis*. He had also received a specimen of what was supposed to be the Loxa species from Mutis at Santa Fé, and included this in his description. Humboldt showed later that Mutis' specimen was not identical with that drawn by La Condamine, indeed quite different, and that Linnaeus had achieved a composite description, without knowing it, of the species called by Humboldt and Bonpland *Cinchona Condaminea* and the *Cinchona cordifolia* of Mutis.³⁵ Howard was led to believe that the species described by La Condamine was the *Cinchona officinalis* var. α and β *Uritusinga* of the present day.

The name of Joseph de Jussieu is linked with that of La Condamine in these first studies in cinchona; he furnished the latter notes to aid him in his investigations about Loxa. After La Condamine's departure, he extended his botanical researches in South America, exploring the country in the neighborhood of Loxa and Zaruma, gathering a great number of specimens among which was one of a tree which was subsequently believed by Vahl to be the one named by him *Cinchona pubescens*; Jussieu was a hardy explorer, spurning neither difficulty nor danger. He went on foot to the province of Canelos, visited Lima in company with Godin, and travelled over Upper Peru as far as the forests of Santa Cruz de la Sierra. Incidentally, he was the first to send to Europe specimens of the coca plant. His end was tragic. His large collection of specimens gathered during fifteen years of laborious research was stolen by a servant at Buenos Ayres, who thought that the boxes contained money and other valuables. This was a blow to Jussieu, who returned to France in 1771 deprived of his reason. In his honor Weddell subsequently gave the name *C. Josephiana* to the shrubby variety of *Cinchona Calisaya*.

In the time of La Condamine, and up to 1770, the only cinchona bark known to commerce came from Loxa and its vicinity, although La Condamine mentions bark from Rio Bamba and Cuença, in the province of Quito, and from Ayavaca and Jaen de Bracamoros. That there grew valuable trees of the cinchona

³⁵ Humboldt, l. c. p. 64.

species around Huanuco and in the province of La Paz, in the interior of Peru, he did not know. It was not supposed that cinchona trees grew north of the equator. Most of these discoveries were reserved for future explorers; but before more extensive researches were undertaken it was found that the genus grew abundantly to the north, in what was then known as the Kingdom of New Granada, now Colombia, and the discoverer was again a man who was not a professed botanist.

Miguel de Santisteban was Superintendent of the mint at Santa Fé, and had had considerable experience in the bark trade. In 1752 he was sent to Loxa by the Spanish Government to effect the organization of the commerce in cinchona bark. On his return from Loxa to Santa Fé he recognized the cinchona tree, called the *Palo de Requeson*, at Popayan and at other places from Loxa to $2\frac{1}{2}$ degrees north latitude. In his official report to the Viceroy he stated that he had also found the trees at Juanambo, north of Pasto, in the forest of Barruecos, between the Citio de Carrales and Guanacas, and he further cites in general the district between Quito and Santa Fé as abounding in cinchona. He brought specimens of the bark with him for the inspection of the botanist Mutis, who visited Santa Fé in 1761.³⁶ "Since my arrival at Bogota," Mutis is quoted as writing by Triana, "I have formed some ideas of this genus (*Cinchona*) from specimens which had been presented to me by the learned Santisteban, Superintendent of the Mint, whose oral and written information made me acquainted with everything concerning this branch of commerce." Santisteban's discovery was of great commercial importance, for the cinchona trees were rapidly disappearing in the Loxa district, and their existence in the north proved an additional source of the drug. Although Mutis acknowledged Santisteban's discovery and the information he himself derived from Santisteban in 1761, he, fifteen years later, claimed the discovery for himself, and thus started a controversy which was one of the bitterest in the history of science.

José Celestino Mutis was born at Cadiz, April 6, 1732. He studied at the University of Seville, where he took his bachelor's degree in 1753, receiving his diploma in medicine at Madrid in

³⁶ Triana, Jose. *Nouvelles études sur le quinquinas*. Paris, 1870. p. 3.

1757, where he resided for a time as a medical practitioner. It was here that he was chosen by the newly appointed Viceroy of Nueva Granada to accompany him to his viceroyalty in the capacity of physician. Mutis was interested in botany, a science which was at that time necessary to the equipment of every physician, and he reflected that a period of sojourn in South America would afford him a rare opportunity for studying the flora of that country. He disembarked with the viceroy and his suite at Cartagena in 1760 and settled down at Bogota, the capital of the viceroyalty, where he at once set to work upon the collection for a Flora of the country which he proposed to write. He varied his medical practice with his botanical studies, making a number of journeys of greater or less duration until, in 1772, he resigned his medical appointment and entered a religious order. This, however, did not interfere with his scientific zeal, for the following years, up to the time of his death, were filled with important researches. In 1783 Charles III, King of Spain, commanded a botanical expedition for the exploration of the Kingdom of New Granada, of which, at the recommendation of Don Antonio Caballero y Gongora, Mutis was appointed director-in-chief. A similar expedition had been formed in 1777 for the exploration of Peru and Chile, to which Ruiz and Pavon were appointed botanists. The direct organization of the new expedition was effected by Mutis, who drew to himself a number of young South Americans as scientific assistants and to make drawings of plants. This appointment he held until his death in 1809. In addition to his botanical work he established, at the solicitation of the Government, a museum of natural history, first at Mariquita and later at Santa Fé. In 1793 his long residence in a tropical climate began to affect his health, and he thenceforth turned his attention to the collection of plants in the more salubrious regions of high altitude, settling at Bogotá after having frequently changed his residence according to the exigencies of his explorations. At Bogotá he founded an astronomical observatory, by order of the Viceroy, and it was in this town that he entertained Humboldt and Bonpland on their visit to South America. He died September 2, 1809. Mutis' researches on the plant life of the Cordilleras gained him a deserved reputation

among the scientific men of Europe, perhaps second to that of Linnaeus himself. He collected a museum of 24,000 plants, 5000 drawings of plants by his pupils, and many shells, minerals, woods, resins, and skins of animals, all which, together with his manuscript, were sent to Madrid. The collection arrived in 105 boxes, which were sent to the botanic gardens, where for some reason, perhaps lack of room, they were deposited in a tool house and remained there, neglected for a number of years.³⁷

In his quinological investigations, which were of some importance, although probably over-estimated in his own time, Mutis received valuable assistance from his pupils Caldas, Zea, and Restrepo, who continued them after his death. His first observations were published in a local paper of Santa Fé, the 'Diario,' in 1793-94, with the title 'El Arcano de la Quina,' and reprinted at Madrid in 1828. An additional part to the 'Arcano,' containing the botanical description of the cinchonas of New Granada, remained forgotten until 1867, when Markham rescued it from oblivion and published it under the title 'Cinchona Species of New Granada.' In 1870 Triana published in his 'Nouvelles Études sur les Quinquinas' the drawings that originally accompanied these descriptions.

The discovery of the medicinal cinchona barks of New Granada, north of the equator, led to a controversy which lasted several years and in which the spirits became heated on both sides. Its origin was this:—In a report to the viceregal Government, presented in 1776, Mutis claimed that in 1772, while riding through the forest of Tena, some twenty miles distant from Bogotá, in company with his friend Don Pedro Ugarate, he first discovered the cinchona plants of the region. This claim was challenged by Don Sebastian José Lopez Ruiz, a physician of Santa Fé de Bogotá, who stated that while on a visit to Loxa he had shown specimens of cinchona bark to Jussieu, and that while travelling through Honda, in Bogotá, he found cinchona trees long before Mutis came into the country. In 1776 Lopez sent specimens of his cinchonas to the viceroy at Santa Fé, and, the Government, rightly conceiving the discovery to be of great importance, granted him a pension. The scientific standing and influence of

³⁷ Markham, *l. c.* p. 45.

Mutis and his partisans afterward induced the Government to think that it had been too hasty, and it withdrew one half of Lopez' pension. Later the other half was withdrawn also, whereupon Lopez went to Spain, presented his case, and succeeded in obtaining an allowance from the Government of 1000 piastres per annum. In 1802 he published a pamphlet entitled 'Defensa y Demonstracion del Verdadero Descubridor de las Quinas del Reyno de Santa Fé, con Varias Noticias Utiles de Este Especifico, en Contestacion á la Memoria de Don Francisco Antonio Zea. Su Autor el Mismo Descubridor Don Sebastian José Ruiz,' Madrid 1802.³⁸ Zea and Caldas, both pupils of Mutis, joined in the fray in support of their master, while Ruiz and Pavon were arrayed on the other side. The victory for a time remained with Mutis, due unquestionably in a great measure to the support of Humboldt, who attacked Lopez in terms unmeasured and wholly unjustifiable.³⁹ It was not until Triana, in 1870, assembled all the evidence on both sides and subjected it to a critical and impartial discussion that Lopez received the justice that was his due. The matter is of sufficient interest to justify a transcription of a part of Triana's presentation of the claims of Mutis and his adherents and his rejection of them in favor of Lopez.⁴⁰—"It is incontestable," he says, "that botany owes to Mutis the description of several species of cinchona native to New Granada and classified by him under the genus *Cinchona*. But the first discovery of the cinchonas in the regions of the northern hemisphere, that is, regions from which they could be exported to Europe without doubling Cape Horn, cannot be claimed for him. The first traveler to recognize, at Popayan, the cinchona tree, called '*Palo de Requeson*,' was Don Miguel Santisteban who, in 1752, came to Bogotá from Loxa, where the Spanish government had sent him to organize the commerce in cinchona. He also found cinchonas at Juanambu, north of Pasto, in the forests of Barruecos, between el Citio de Corrales and Guanacas. 'Since my arrival at Bogotá,' says Mutis, 'at the commencement of 1761, I have formed some ideas of this genus from specimens which

³⁸ Markham, *l. c.*, p. 46.

³⁹ Humboldt, *l. c.*, p. 64.

⁴⁰ Triana, *l. c.*, p. 4.

were presented to me by the learned Santisteban, superintendent of the mint, whose oral and written information made me acquainted with everything concerning this branch of commerce.”

In spite of the information thus obtained by Mutis in 1761, it was not until fifteen years later that he made use of it, when he claimed for himself the discovery of the officinal cinchona in New Granada. It was in August, 1776, that Don Sebastian José Lopez presented to the Viceroy, at Santa Fé, two parcels marked A and B, containing specimens of cinchona which he had discovered. Mutis was charged with the examination of them, and, having studied them, he addressed to the Viceroy a report in which he declared that the two plants collected by Lopez were cinchonas, and that they might represent two species, or at least, might be considered as two varieties of the same species; he added that the respective values of their barks could be determined only by medical tests; he affirmed that the plant represented by specimen A came from a region more elevated than that in which grew the plant represented by specimen B. It is in this report, important because of the occasion on which it was produced, that Mutis for the first time bases his claim to the priority of his discovery of cinchona in the neighborhood of Bogotá, fixes the date and states the circumstances which accompanied it. Triana continues:—

The 15th May, 1770, in reply to questions which Linnaeus had put to him, Mutis expressed himself in a fashion which appears to confirm the surmise that up to that time, 1770, he had not discovered the true cinchonas. “You ask,” he writes, “if the young branches of cinchona are lactiferous, and in what soil and at what degree of temperature they grow. I confess my ignorance on these matters. I have never visited the province of Quito, where the cinchonas appear to be native, nor Caxanuma, Loxa and Cuença, because of the great distance which separates these places from the district of Cartagena, Bogotá, Pamplona, Giron. I am inclined to the belief that those plants grow upon very high mountains, and yet it seems that the *Cinchona officinalis* is not subjected to this degree of temperature except in the province of Quito from the equator to 5 degrees south latitude. M. Santisteban has, however, assured me that the cinchonas are found at the second degree of north latitude, about Popayan, and that he himself has gathered the cinchona in flower in that region as *Palo de Requeson*. He has given me some of its leaves, which are twice as large as those of *Cinchona officinalis*, of which I have not seen the flowers but which, he says, have six stamens. I send with my letter the description of another cinchona which I have named *gironensis*.”

The following is from the report mentioned, which bears no specific date but

was written in August, 1776, according to Lopez, and in which Mutis alleges to the Viceroy his discovery of the cinchonas of Bogota. "Certainly," writes Mutis, "the Quinquina contained in parcel A resembles in all its characters the best Quinquina of Loxa, of which, on my arrival in that region, in 1761, Don Miguel de Santisteban had been so good as to give me specimens—leaves, flowers, and fruits—preserved in paper envelopes. I had, since then, made the most painstaking researches, without result, to discover *Cinchona* in that neighborhood by directing my steps beyond the fifth degree of north latitude, when, travelling with Don Pedro Ugarte, I found them, in 1771, in the forest of Tena, and the following year in the forest of Honda. I found the tree which I had the honor to present to the notice of Senor Manuel Guirior, Your Excellency's predecessor, with the same zeal that animates Don Sebastian Lopez today."

However, the 6th June, 1773, that is, two years after his alleged discovery, Mutis, writing to Linnaeus, says: "I am very grateful to you for the honorable mention which you accord me in connection with the genus *Cinchona*." (Linn. *Syst. Plant.* ed. 12, tom. II, 164)." It is strange that in this letter there occurs no word regarding the discovery of the cinchona, a fact, which Mutis must have known, would be of supreme interest to Linnaeus.

Another surprising circumstance is that, informed as he was since his arrival at Bogotà, by Santisteban regarding the existence of the *Cinchona*, being in possession of specimens and drawings of the plants and having for a considerable time travelled through the cinchona-bearing district, Mutis, according to his own statement, had not recognized the cinchonas before the years 1762 and 1772. This fact has not escaped the attention of Lopez, who comments on it in these terms:—"Mutis landed at Cartagena in 1761, went up the Magdalena River and followed the route of Opon to go to Port Real de Velez. In this course are encountered a large number of cinchona trees, as also at Monte del Morro, where Mutis passed without seeing any. He arrived at Santa Fé, where Don Miguel Santisteban presented him with leaves, flowers and fruits of the cinchona of Loxa and also communicated to him his own observations. In the following year, 1762, he returned to Cartagena by the road which crosses the extensive forest of Honda, prolific in cinchonas of all species. He is a botanist, he is in possession of specimens and yet, during a journey of four days he has seen nothing! He often went on foot to the famous Salto de Tequendama; in the forest which environs it and along the path which it is necessary to follow on foot in order to arrive at the edge of the abyss, the cinchonas crowd—and he never saw them! In 1766 or 1767 he went to the silver mine La Montuosa, made botanical excursions into the mountains—he himself tells us this—and in his four years' residence, that is, up to 1770, he did not even suspect the existence of cinchonas!"

However all this may be, the rival claims of Mutis and of Lopez led to a bitter controversy. The question can be settled only by an appeal to unquestionable dates. But Mutis had on his side scientific renown; he appealed to the testimony of the viceroy and learned men; he had furthermore the support of Humboldt; all this gave him the advantage and Lopez, defeated and his claims rejected, had the misfortune to lose, wholly or in part, the pension of 2000 piastres which the Spanish Government had rightly granted him.

The controversy, be it noted, was not over the discovery of the New Granadan cinchonas in general but of those that yielded

efficient, commercial bark. "Now," says Triana, "it has been ascertained that there grows in the western Cordillera, from Bogota to Popayan, but one cinchona which satisfied the condition: this is the cinchona called *tunita*, or *Tuna de Fusagasugá*. The other barks confounded under the name of *Cinchona* can only cause trouble in therapeutics and fraud in commerce. In the matter of the controversy between Lopez and Mutis it therefore becomes necessary to determine, if possible, who was the first to discover or report the discovery of the *tunita* or *Tuna de Fusagasugá*. I regret that I have been unable to find a single bit of documentary evidence in favor of Mutis on this point, but that the advantage is all on the side of Lopez."⁴¹

In fact, the eastern slope of the Cordillera of Bogota where the *tunita* (*Cinchona lancifolia*) grows, was not explored by Mutis before his removal to the capital. He confined his expeditions to the western chain of the mountains, at the upper part of the Magdalena River, near Mariquita, Tuna, and Honda, where, according to Triana's own experience, no true cinchona grows. The supposed cinchona found by Mutis in this region in 1771 was one of the "false cinchonas," called *Cascarilla* by Weddell, probably *Cascarilla magnifolia*. The "cinchona" which Mutis collected in the province of Pamplona, northward of Santa Fé, in 1766 is, according to Triana, *Cosmibuena obtusifolia* Ruiz et Pavon, which does not yield a febrifuge bark. All the true cinchonas contained in the 'Quinologia de Bogotá' of Mutis and named by him *Cinchona lanceolata* and *Cinchona cordifolia* were discovered by Santisteban, Lopez, or Mutis' nephew, Sinforio,—not one by Celestino Mutis himself.⁴²

Toward the end of the eighteenth century the Spanish Government prosecuted with zeal the search for cinchona trees in regions hitherto unexplored, and it was rewarded by the discovery of additional valuable species. The rapid disappearance of the Loxa trees was thus offset by fresh sources of supply. In 1777 Hippólito Ruiz and José Pavon were appointed to direct an expedition for the exploration of southern Peru and Chile. Accompanied by the French botanist Dombey and two artists

⁴¹ Triana, l. c. p. 8.

⁴² Markham, l. c. p. 47; Triana, l. c. p. 8.

named Brunete and Galvez, Ruiz and Pavón left Cadiz, November 4, 1777, and reached Callao April 8, 1778. In the neighborhood of Lima they collected a large number of plants and sent to Spain 300 dried specimens and 242 colored drawings. Crossing the Andes they continued their explorations in the forest of Tarma, whence they proceeded to Huanuco. On the hill of Cuchero or Cocheros, not far from Huanuco, they discovered seven species of cinchona trees, and thereupon returned to Lima. They then proceeded to Chile by sail, exploring the greater part of that province, after which they again went to Lima. These botanical collections were packed in fifty-three cases and shipped to Spain on board the *San Pedro de Alcantara*; but that vessel was shipwrecked off the coast of Portugal in 1786 and the fruit of so many strenuous labors was lost. At about this time also M. Dombey returned to France, and Ruiz and Pavon continued their researches without his assistance. Returning to Huanuco, Ruiz and Pavon explored the course of the rivers Pozuzu and Huancabamba, after which they settled for two months at the hacienda of Macora, near Huanuco. Their companions here were Don Francisco Pulgar and Don Juan Tafalla, who, by order of the King, joined them as associates, Pulgar in the capacity of artist, Tafalla as botanist. Here bad luck again overtook them, for in August, 1785, their house was destroyed by fire and their collections and journals perished in the flames. Nothing dismayed, they set forth on a new expedition, journeying through the forests of Muña, Pillao and Chacahuasi, where they occupied themselves in examining the species of cinchona that they found there. Finally, April 1, 1788, they sailed from Callao and arrived at Cadiz in September. Again settled in Spain, Ruiz published in 1792 the 'Quinologia,' to which was added, in 1801, a supplement in the composition of which Pavon collaborated, and which contained the most important results relating to the cinchonas. From 1798 to 1802 the two explorers were engaged in the composition and publication of their *magnum opus*, the 'Flora Peruviana et Chilensis.' A work entitled 'Nueva Quinologia' was written between 1821 and 1826 but remained unpublished; the manuscript came into possession, thirty years later, of Mr. John Eliot Howard, the English quinine manufacturer, who made it avail-

able to scientists by publishing it with twenty-seven colored plates most of which had been drawn from Pavon's specimens housed in the herbarium at Madrid.

The researches of Ruiz and Pavon were continued in the province of Huanuco and in Chile by their pupil Tafalla, assisted by Mancilla. In 1792 Tafalla discovered in the forests of Monzon and Chicoplaya the species *Cinchona micrantha*. At about the same time that Ruiz and Pavon were beginning their explorations in southern Peru, Don Francisco Renquifo (Renquizo, Renjifo) found cinchona trees in the province of Huanuco, in the central part of Peru, in the mountains of San Cristobal de Cuchero. Caldas and Zea, the most distinguished of the pupils of Mutis, continued the work of their master and made important contributions to the natural history of the cinchonas.

Francisco José de Caldas was a South American, born at Popayan in 1770. His interest in science dated from his early youth, and he devoted himself assiduously to the study of mathematics, physics, meteorology, physical geography, and botany, all these sciences serving him to good purpose in his exploration of the cinchona forests. He was also a skilled mechanician, constructing many of the instruments which he employed in his scientific work. It is probable that many of the results of his observations were calmly appropriated by Mutis, for Caldas later complained bitterly that that botanist had failed to accord him due recognition for his services. Caldas was appointed a member of the botanical expedition of 1802 and for several years devoted himself to the study of the natural history and distribution of the cinchona species. In 1803 he explored the forests of Malbucho whence he proceeded to Ynlac, on the western slope of the Cordilleras. He afterward explored the mountains of Alausi, Cibambe, Pante, Jaday, and Gualacco, in the neighborhood of Cuenca, and finally the district of Loxa. In these expeditions he described twenty-two species of cinchona.

The Viceroy of Peru, the Baron de Carondelet, commissioned Caldas to communicate officially the results of his observations, which was done in a memoir entitled 'Memoria sobre el estado de las quinas en general y en particular sobre la de Loxa.' This was accompanied by a map of the elevations at which the various

cinchonas grow and also cross-sections of the cinchona ravines in the Quito district. About two years later the manuscript of this report, together with the botanical descriptions and drawings, was purchased by M. Henri Ternaux, at the time resident at Popayan as attaché to the French embassy to Colombia. Unfortunately the map mentioned was not contained in this collection and was never published. Ternaux communicated the memoir to Dr. Martius, who presented it before the Royal Bavarian Academy, held at Munich, May 9, 1846, accompanying it by a commentary.⁴³ Caldas left many other memoirs on various scientific subjects, many of which do not appear ever to have been published. His scientific career closed only with his life, which came to an end too soon, October 30, 1816. He was an ardent patriot, and espoused the cause of South American independence. He was taken prisoner and executed by the Spanish general Murillo.⁴⁴ Caldas' attempt to fix the geographical boundaries of the genus *Cinchona* was only partially successful, but this lay in the nature of the case, for the enterprise was beyond the power of a single man, especially in those days of difficult travel. His observations, however, were accurate as far as they went and proved to be of great service to later explorers.

Francisco Antonio Zea was also a South American by birth, a native of Antioquia. At an early age he came to Bogotá, where he became associated with Mutis who, in 1793, sent him on a botanical excursion to Fusagasugá. He went to Spain in 1795 where he published a memoir on the cinchona species. He became involved in an acrimonious controversy with Ruiz and Pavon over the question of the identity of the New Granada cinchona species with those of Loxa. He maintained that they were the same, in which he was wrong. His polemic, entitled 'Memoria sobre la quina segun las principios del Señor Mutis' appeared in the 'Anales de Historia Natural de Madrid' in 1800.⁴⁵ He was also involved in the Mutis-Lopez controversy.

The investigations made by Humboldt and Bonpland in the cinchona districts, particularly those about Loxa, were of great

⁴³ Martius, *Pharmaceutical Jour.*, VII, 1848, p. 88, 184.

⁴⁴ Markham, *l. c.* p. 46.

⁴⁵ Zea, *Ann. Hist. Nat. Madrid* 1800, II, No. 5, p. 196.

importance in that they helped to clear up in a great measure the confusion that existed in the description of a number of the species of cinchona. Humboldt's purpose was to study the trees on the spot, their botanical characters, geographic distribution, relation to elevation and climate, etc. Humboldt had intended proceeding by sea from Cartagena to Quito by way of Panama to Guayaquil, but hearing at Cartagena that the winds were unfavorable and that the journey might occupy two or three months, he changed his plan and decided upon the inland route up the Magdalena River. This gave him the opportunity he desired of crossing the Andes as well as of visiting Mutis in Santa Fé, with whose collection of plants he was desirous of comparing those collected by himself and Bonpland.⁴⁶ After a stay of three weeks at Cartagena he left Turbaco April 19, 1801, and embarked with Bonpland on the Magdalena River at Barancos Nuevos, April 21. His journey to Honda, up the Magdalena, lasted fifty-five days. There the two naturalists found cinchona forests. On their arrival at Santa Fé they were received with great ceremony, both on their own account and because it was known that they were on their way to Mutis. The veteran botanist, then in his seventy-fourth year, received them with great cordiality and conducted them to a house which he had prepared for them in his own neighborhood. Bonpland became ill, which caused the travelers to be delayed at Santa Fé till the eighth of September when they set out for Quito westward across the Magdalena River through Contreras to Ibagué. They then crossed the eastern spur of the Cordilleras by the pass of Quindiu, spent the month of November at Popayan, and then crossed to Pasto, reaching Quito, January 6, 1802. In the autumn of that year they took the road to Loxa in order to complete their investigation of the cinchonas.⁴⁷

Humboldt and Bonpland's observations on the botany of the countries visited by them were published in the '*Plantes Equinoctiales*,' in which they received signal assistance from Willdenow in the identification of species. The results of his studies of the cinchonas were published by Humboldt in two papers entitled '*Ueber die Chinawälder in Südamerika*' which appeared in

⁴⁶ Humboldt, *l. c.* p. 58.

⁴⁷ *Ibid.*, p. 58.

'Der Gesellschaft naturforschender Freunde zu Berlin Magazin für die neuesten Entdeckungen in der gesammten Naturkunde.' In these papers Humboldt subjected the published results of previous investigators to a critical examination and revision. At that time quinologists were engaged in a heated controversy over the position of the so-called "genuine" cinchona of Uritusinga which La Condamine had described in 1738, some identifying it with the Peruvian *Cinchona nitida*, others with the *Cinchona lancifolia* of Mutis; in this controversy Zea was involved on one side and Ruiz and Pavon on the other.⁴⁸ Humboldt pointed out that the question could be laid at rest only by one who had visited the cinchona regions of Loxa and studied the subject on the spot, and that as none of the parties to the controversy, Mutis, Zea, or Ruiz, had entered the province of Loxa, the discussion was without point. As he demonstrated, in fact, from the time of Joseph de Jussieu no explorer had visited the mountain plateaus until Humboldt and Bonpland undertook the journey for the express purpose of securing trustworthy information; and Humboldt therefore claimed, justly, that he had a right to be heard on these matters.⁴⁹ He and Bonpland gave the proof in the 'Plantes Equinoctiales,' second fascicle, that the *cascarilla fina de Loxa*, the cinchona of Uritusinga, was altogether different from the *Cinchona lancifolia* of Mutis and from all the Peruvian species described in the 'Flora Peruviana' and the supplement to the 'Quinologia.' They proved, also, that Linnaeus' description of the species which he called *Cinchona officinalis* was a composite, based upon the one of Loxa which Humboldt and Bonpland called *Cinchona Condaminea*, and the other, of New Granada, the *Cinchona cordifolia* of Mutis; Linnaeus' mistake arose from Mutis' sending him a species which he believed to be the one yielding the Loxa bark but which bore no resemblance to the plant drawn by La Condamine.⁵⁰

The uncertainty prevailing in the distinction of species Humboldt ascribes in great part to the fact that botanists had paid too much attention to the forms of the cinchona leaves, which

⁴⁸ Humboldt, l. c., p. 58.

⁴⁹ *Ibid.*, p. 59.

⁵⁰ *Ibid.*, p. 61.

vary considerably even in plants of the same species. "Indeed," says he, "I know of no tree that varies more in the form of its leaves than the cinchona. He who studies dry herbarium specimens and has not had the opportunity of observing the plant in the field will suppose, judging leaves even of the same twig, that he is dealing with different species. The yellow fever bark, *Cinchona pubescens* Vahl, we have found to bear at the same time ovate, oblong, ovate-lanceolate, and ovate-cordate leaves. Mutis called it *cordifolia* because it is the only species upon which cordate leaves are at times found. The lance-leaved *Cinchona Condaminea* itself, the finest cinchona of Uritusinga, possesses, according to the elevations at which it grows, leaves of the greatest variety of form; it would deceive the *cascarilleros* if they did not recognize the tree by the glands which were so long overlooked by botanists"; and, he goes on to say: "The more cinchona trees vary in the form of the leaves, according to their habitat, the climate, the occurrence of the trees in isolation or surrounded by other trees, the more necessary it is to pay attention to the character of the flowers, particularly to the length of the stamens, the relation between stamens and anthers, and the adnate or free parts of the filaments. It is not sufficient to divide the species into such as have a smooth or hairy capsule, *stamina exserta* or *inclusa*. An attentive botanist will find in almost every kind differences in the structure of the corolla."⁵¹

Humboldt's researches led to results that were of practical as well as scientific importance. They enabled him to point out that a number of barks which had passed in commerces as cinchona were not cinchona at all, although they possessed febrifuge properties. Among these, later called "false cinchonas," was one which the Capuchin monks of the missions on the river Carony were the first to make known, called *Quina de la Guayana* or *de la Angostura*, and which Mutis, who had used it with success in his medical practice, having become acquainted with it in Spain in 1759, had already suspected not to be a cinchona. The tree yielding this *Angostura* bark was known as the *Cuspare tree*; Humboldt and Bonpland studied it and recognized in it a new genus to which Willdenow gave the name *Bonplandia*.⁵² The

⁵¹ Humboldt, *l. c.*, p. 105.

⁵² *Ibid.*, p. 107.

cascarilla de Nueva Andalusia, also known as *cinchona de Cumana*, was a bark which had been sent to Europe four or five years before Humboldt's visit to South America on the supposition that it was a cinchona, which it was not. The so-called "cinchona bark of Acatamez" came from the place after which it was named, a village lying westward of the Villa de Ibarra on the Pacific coast between Rio Verde and Rio Esmeraldita; it was not a cinchona. The genus *Cosmibuena* of the 'Flora Peruviana' yielded barks of slight febrifuge virtues, and it was to this genus that the *Cinchona longifolia* of Mutis and the *Cinchona grandiflora* of Ruiz belonged. Humboldt thus helped to clear the situation by assigning a number of so-called "cinchonas" to their proper places; but the final decision respecting "true" and "false" cinchonas was not given until Weddell investigated the entire subject anew more than forty years later.

Extensive investigations of the cinchonas were carried on by the distinguished German botanist Dr. Karsten, who, landing at Puerto Cabello, in Venezuela, in the spring of 1844, spent twelve years in South America in travel. He found cinchona trees growing near Caracas, on the southern slope of the thickly wooded mountains of Tovar. In 1852 he met with the *Cinchona lancifolia* of Mutis—the *tunita*—on the table-lands of Tunja, in Colombia, and near Popayan he discovered another variety of the *tunita*, known as the *Calisaya de Santa Fé*.⁵³ Karsten's botanical descriptions and some of his plates were published by Markham in 1867. Karsten, however, included many species which were later shown not to belong to the genus *Cinchona*. The Huanuco district had been studied by Dr. Poeppig, who travelled in Peru and Chile between 1827 and 1832. He stated that the Huanuco barks had fallen into discredit, as had those of New Granada, owing to the adulterations practiced by small speculators, and that after 1815 the commerce in them had practically ceased. Thaddaeus Haenke must also be named among the pioneers of quinological research; it was he who, in 1776, with the naval officer Rubin de Celis, drew the attention of the inhabitants to the valuable forests on the eastern slopes of the Bolivian Andes, which yielded the highly prized *Cinchona Calisaya*.

⁵³ Markham, *l. c.*, p. 48.

The classic in the literature of cinchona is without question Weddell's 'Histoire Naturelle des Quinquinas,' published in Paris in 1849, representing the rich fruit of his explorations of two years' duration in the forests of Bolivia and southern Peru. Like Humboldt, Weddell had for a long time been dissatisfied with the published classifications and descriptions of the cinchona species generally accepted by scientific men, careful examination of the literature and of specimens in herbaria having convinced him that botanists had been altogether too lax in defining the limits of the genus. He writes:

Established by Linnaeus in 1742, who based his conclusions on the description given by La Condamine, the genus *Cinchona* in the beginning comprised two species, the *Cinchona officinalis* and the *Cinchona Caribaea*, the latter now classified as an *Exostemma*. Represented at the very first by two species so remote from one another, it is not surprising that the genus should have increased rapidly by the discovery of new species. Vahl, who came immediately after Linnaeus, described nine species of *Cinchona* and Persoon in his *Synopsis* mentions twenty-one, which Lambert, in the second edition of his memoir *Illustration of the Genus Cinchona* increased by a few more. If, now, the genus had been kept within the original limits, the number of species composing it would have been quintupled by the extensive discoveries made by subsequent explorers; but it was soon perceived, thanks to the large quantity of material available for comparison, that the genus was loaded with elements too heterogeneous, and efforts were made to correct it; it was not, however, confined to its true limits until De Candolle undertook the task, who was the first to insist upon the mode of dehiscence of the capsules of the true cinchona *a basi ad apicem*.⁵⁴

Of De Candolle he says that, "in doing this he was but re-establishing a characteristic given by Linnaeus, but he was not more consistent than Linnaeus in adhering to it, for he describes as *Cinchona* several species whose fruits split from top to bottom, species which Endlicher has placed in a sub-genus *Cascarilla*."

Another matter which, in his opinion, required elucidation was the question of the alleged identity of the cinchonas of New Granada with those of Loxa, a question which had led to the controversy between Zea on the one hand, and Pavon and his followers, on the other. That controversy had failed to settle the question one way or the other. Then, again, was the need for fixing the geographic, topographic, and climatologic boundaries of the cinchona-producing regions, a task which had been achieved in part by Caldas and Humboldt but which still exhibited ex-

⁵⁴ Weddell, l. c., p. 16.

tensive gaps. Finally, it was important to learn the botanic origin of the various kinds of bark offered in the market, a subject upon which opinion was at variance. It was with these problems in mind that Weddell gladly availed himself of the opportunity to study his material on the spot so far as this was possible, when he was appointed to accompany as botanist the scientific expedition sent out by Louis Philippe in 1843 under the command of the Comte de Castelnau for the exploration of those regions of South America that were still wholly or partly unknown to European scientists. The expedition sailed from Brest, made a short stay at Senegal, and finally landed, in the middle of June, at Rio de Janeiro, whence it soon left for the interior. More than two years were spent by Weddell with de Castelnau in the forests and deserts and on the rivers of Brazil. A special mission with which he had been entrusted by the Museum of Natural History of Paris caused his separation from the main body of the expedition; he parted from his companions at Mattogrosso, on the Paraguay River in May, 1845, and, after a brief visit to the Ipeco-cuanha regions of Brazil, directed his steps to the frontier of Bolivia.⁵⁵

Weddell entered Bolivia at Campos, August, 1845, going by way of the country of the Chiquito Indians. Here he learned that the Chiquitos possessed a remedy which they prized as a "fever bark"; it was not, however, a cinchona but a species of *Gardenia*, which Weddell named *Gardenia Chiquitensis*. No cinchonas were found in this district, for the nature of the country was quite unfavorable to their growth, being low, flat, and, in the rainy season, subject to inundation; nor was Weddell able to obtain any information regarding the cinchonas until he reached Santa Cruz de la Sierra, where certain rumors induced him to turn to the south. At the end of November he gained the Rio Grande, passing by way of Piray and Abapo, and then proceeded by the Cordillera province of Azero and the plateau of Pomabamba and the province of Cinti to Tarija, where he arrived at the end of January, 1846. This journey, which he later pushed to the east as far as Gran-Chaco was, Weddell tells us, one of the most difficult and painful that he had ever undertaken; but the result repaid the labor—he

⁵⁵ Weddell, *l. c.* p. 4.

reached the southern limits of the cinchonas, naming the species which he found at the nineteenth parallel of south latitude *Cinchona australis*. At Tarija he was told by the natives of a wonderful fever bark, which, however, again turned out not to be a cinchona, in fact not even a plant of the *Rubiaceae*. In the beginning of August he visited the large towns of Bolivia—Potosi, Chuquisaca, and Cochabamba—in none of which he found commerce of cinchona bark to be carried on, the centre of trade of the region being La Paz. To reach this town by the interior valleys he proceeded near the great chain of the Andes through the provinces of Ayopaya, Enquisivi, and Yungus; he traversed a long and beautiful series of terraces which he gradually descended, passing by stages through all varieties of climate and beholding all the kinds of vegetation corresponding to them. “Les différentes espèces de Cinchona se multipliaient ici sous mes yeux.”⁵⁶ It was upon his entrance into the province of Enquisivi that he found the tree, up to this time unknown, which yielded the precious Calisaya bark, and to which he assigned the name *Cinchona Calisaya*. He found the province of Ayopaya to be almost destitute of forest vegetation and torn by violent torrents, but toward the north the scenery changed its character and at Palca he learned of the discovery on the banks of the river Ayopaya of an immense forest of cinchonas which had not yet been attacked by the axe of the *cascañeros*.⁵⁷

One of Weddell's objects had been the gathering of information regarding the collection and preparation of the barks and their commerce and sophistication, but it was not until he reached the province of Yungus, the richest and most fertile of Bolivia, that he obtained the first precise information. In order to add to the knowledge gained here, he travelled to the towns of Yrupana, Chulumani, Coroico, and others, all important centers of the cinchona, as well as of the coca-trade. Quitting Coroico, he crossed the Andes to La Paz, where he stayed a short time, proceeding thence to Puno, Arequipa, and the environs of Lake Titicaca. In all these places he found abundant opportunity to study the barks which came thither from various localities; the

⁵⁶ Weddell, *l. c.* p. 5.

⁵⁷ *Ibid.* p. 8.

rainy season of 1847, when it was difficult, indeed almost impossible, to travel, was devoted to the study of cinchona economics. He resumed his route as soon as the weather permitted, making almost the complete circuit of Lake Titicaca, his intention being to explore first the province of Larecaja and then to proceed to Caupolican or Apolobamba. He had expected to find the town of Sorata or Esquibel, situated on the western slope of the Andes and at the foot of one of the highest peaks, one of the most active of the centers of the cinchona trade, for such was the common opinion, but it turned out to be only a point of transit for the product of the valleys of the interior. It was to these valleys, therefore, that he directed his steps. He passed over the snows of Illampo, where the auriferous Tipoani has its source; he followed a frightful road along the ravine to the village of Tipoani, which he calls "a pestilential place" inhabited by gold-washers but also an active bark center although the large trees were disappearing from the region.⁵⁸

Weddell's next objective was the still virgin forests of the river Mapiri of which he had heard much spoken. He therefore had a raft constructed at a neighboring mission, and embarking upon this passed the rapids without accident and landed at Guanai, a village of the Lecos Indians. After visiting the mountains of the Tumache he continued his course up the Mapiri, traversed the forests, and finally reached Aten and Apolobamba, worn out by fatigue and overcome by the fever common to the regions. Weddell was delighted with the aspect of the country. "*Le pays de ces côtés,*" he writes, "*prend un aspect plus riant, et vraiment, n'était-ce la plus grande inégalité du terrain, on se croirait transporté dans les Campos du Bresil. Les forêts, en effet, ont disparu ou n'occupent que l'horizon; et l'oeil plane partout sur de jolies collines gazonnées, clairsemées d'arbustes ou de petits arbres, et souvent même de charmants bosquets.*"⁵⁹ Several species of cinchona grew here but they were mere shrubs; but the perfume of their flowers was very fragrant. The site of Apolobamba was one almost naked plain; as it was the center of one of the most exploited of the Bolivian cinchona regions the forests had dis-

⁵⁸ Weddell, *l. c.*, p. 7.

⁵⁹ *Ibid.*

appeared. In order to find a cinchona tree, Weddell found it necessary to go a distance of eight to ten days' journey.⁶⁰

Circumstances made it impossible for Weddell to visit, as he had intended, the neighboring Peruvian province of Carabaya, so that he was compelled to go again to the west slope of the Cordilleras. Péléchuco, a cold, gloomy village was the commercial center of this district, as Sorata was that of Larecaja; he arrived at it by the valley of the Tuiche River. At the end of June he finally succeeded in entering Carabaya. This province is divided into two distinct geographical regions, one a plateau, the other a long series of parallel valleys. The greater part of the Peruvian barks exported to Europe in Weddell's time came from this province; he directed his explorations chiefly to the banks of Tambopata and San Juan del Oro which he reached by way of the ravines of Lima and Quiaca. "Il serait difficile," he writes of these forests, "de donner une idée de tous les trésors de végétation ensevelis dans ces solitudes. Le soif de l'or les avait peuplées autrefois, mais la forêt y a repris partout son empire, et la hache du *Cascarillero* en trouble seule aujourd'hui le silence."⁶¹ Weddell's stay here was very profitable, the governor of the province had been in the highest degree courteous and had furnished him with guides who were intelligent, experienced, and in every wise dependable, and Weddell was enabled to make many additions to his quinological collection.

Weddell next proceeded to Sandia and ascended the plateau to Crucero, the capital of Carabaya, which he soon quitted for Cuzco. A final excursion to the beautiful valley of Santa-Ana, in which he was accompanied by the French quinine manufacturer Delondre, and which brought him to the latitudes already explored by preceding quinologists, concluded this memorable expedition. Having traversed South America from ocean to ocean, and having completed a five-years' journey which was one of the most considerable undertaken on the continent, he returned to Europe. Weddell's travels may be indeed regarded as an epic of exploration.

Weddell brought to Paris seeds of *Cinchona Calisaya*, some of

⁶⁰ Weddell, *l. c.*, p. 7.

⁶¹ *Ibid.*, p. 8.

which were placed in the Jardin des Plantes in 1848 and others in the garden of the Horticultural Society of London. They germinated, and many of the plants were given away, some being sent by the Dutch Government to Java. These were the first cinchona trees grown in Europe. Shortly after his return to France, Weddell was appointed *aide-naturaliste* to the Paris Museum, a position previously held by Decaisne, and in 1851 he was entrusted with a fresh mission to South America which enabled him to revisit the forests of Peru. The result of this journey was a collection of additional material on cinchona and a book of travel, 'Voyage dans le Nord de Bolivie et dans les Parties Voisines de Perou,' published in Paris in 1853. In 1848 he published in the 'Annales des Sciences Naturelles' a paper entitled 'Revue du Genre Cinchona,' in which he enumerates the species of Cinchona proper as well as those formerly regarded as cinchonas but which, in his opinion, belonged to the genera *Remijia* and *Cascarilla*, and of a new group which he established under the name *Gomphosia*.

The 'Histoire Naturelle des Quinquinas' appeared in 1849. It is a magnificent work containing, besides the letter-press, plates of the *Cinchona* species, several plates in color of the barks, and a map of the cinchona regions. It is based upon Weddell's own observations in the cinchona forests and on material in the herbaria of Europe, and reviews everything that had been written previously on the cinchonas from the standpoint of botany and exploration. It is divided into two parts, the first dealing with the genus *Cinchona*; in this the characteristics of the genus are fixed, one of which is the content of febrifuge alkaloids. Weddell's study of the organographic and anatomic features of *Cinchona* revealed a number of new facts. A characteristic feature is found in the medullary rays; these being extended considerably in the vertical sense in the wood of the cinchonas and, in fact, of the *Rubiaceae* in general, give them a special character which makes it possible to distinguish the genus by aid of the microscope from most other woods. Again, he found on the ventral face of the leaves, at the base of the stipules, of all arborescent *Rubiaceae* which he studied, curious glands, which he called *glandes stipulaires*; these are composed of a nucleus of

cells in the form of an inverted cone and contain a substance of gum-resinous character. These cells exhibit at times, at their free ends, a slight depression which Weddell at first supposed to be a pore, but subsequent examination showed that the cells are everywhere closed. The cinchona barks particularly claimed Weddell's attention; study of their anatomical structure led him to classify them under three types, the basis being furnished by the nature and proportions of the fibrous and other cellular elements present, their fracture, and the nature of their chemical constituents. Among the interesting facts elucidated by him was the constant parallelism of the anatomic structure and the constituents, so that either one or the other would serve to determine the nature of the bark.⁶² He added eight new species to those admitted by him to the genus *Cinchona*, he cleared up the mystery which had long hung over the botanic origin of the *Cinchona* known as "yellow crown bark"; and, finally, he established the origin and the history of most of the other febrifuge barks that entered the markets of Europe. The geographical distribution of the genus *Cinchona* is treated in the first part of the work also. Up to Weddell's time knowledge of this had been imperfect because of defective information regarding the southern cinchona-bearing regions. Weddell's explorations in Peru and Bolivia filled the still-existing gaps; he was enabled to fix the southern limit and by coördinating the results of his own discoveries with those of preceding workers in the field he completed the geographic map of the cinchona regions. The second part of the 'Histoire Naturelle' treats of a number of genera allied to *Cinchona*, of which many species had been wrongly assigned by botanists to the genus *Cinchona*. Here again, we find the painstaking study of the characteristics of the structure of the external organs and particularly the mode of dehiscence of the capsule, as well as the chemical nature of the tissues.

The general result of the various expeditions into the forests of South America to the middle of the nineteenth century may thus be summed up as follows:—The genus *Cinchona* is native to a region extending from 19° south latitude, where Weddell found the *Cinchona australis*, to 10° north latitude. This region follows

⁶² Weddell, *l. c.*, p. 23.

in general the curve of the Cordilleras of the Andes over a distance of approximately 1500 miles of latitude. The trees and shrubs flourish in a cool and equable temperature, even in the regions about the equator, growing on the slopes and in the valleys and ravines of the mountains, as high as 9000 and never lower than 2500 feet above sea-level. The species are in general confined within narrow belts as regards elevation above the sea and parallels of latitude. The valuable *Cinchona Calisaya*, for example, abounds in Bolivia and the Peruvian province of Carabaya, but it is never found nearer the equator than 12° S. Between that parallel and 10° S. the species encountered are valueless as far as their febrifuge qualities are concerned; but in northern Peru occur the trees from which the "gray bark" of commerce was obtained. In each of these regions limited by latitude, the different species are separated from one another by belts of altitude. This distribution by zonal regions is not absolutely strict, for several of the hardier and stronger species have wider ranges than those mentioned, while the more sensitive, which are usually the most valuable kinds, are confined within their zones and never pass more than 100 yards beyond them. Local circumstances, of course, modify the positions of the zones of the species as regards altitude.⁶³

Under favorable circumstances and in good soil the cinchonas, in their native surroundings, are among the large forest trees; on higher elevations and where the ground is stony, they often grow to a great height before branching, while at the upper limit of their zone they are mere shrubs. The leaves vary greatly in size and form, but in most of the finest species they are lanceolate, bright green, shining, with crimson veins and petioles. The flowers are very small, hanging in clustering panicles, of a deep rose color, paler near the stalk, dark crimson within the tube, the laciniae of the corolla bordered by white, curly hairs. The flowers of *Cinchona micrantha* are white and very fragrant.

In the early years of cinchona research a number of species were reported as having been found in other parts of the world, even in the East Indies;⁶⁴ but subsequent and more careful ex-

⁶³ Markham, *l. c.*, p. 63.

⁶⁴ Humboldt, *l. c.*, p. 61, 64.

amination of their botanical character caused their relegation to other genera:—cinchonas have never been found in other parts of the world outside the limits of the South American regions. This region, beginning at the south, is briefly as follows:—Its beginning is in the Bolivian province of Cochabamba, 19° S., whence it passes through the yungus of La Paz, Larecaja, Caupolican, Coroico, and Munecas, into the Peruvian province of Carabaya; thence it extends through the Peruvian forests, on the eastern slope of the Andes, of Marcapata, Paucartampu, Santa Ana, Huanta, and Uchupampa, to Huanuco and Huamalies, continuing through Jaen, to the forests near Loxa and Cuenca and on the western slopes of Chimborazo. It begins again in 1° 51' N., extending through the province of Popayan and along the slopes of the Andes at Quindiu, reaching its extreme northern limit on the wooded heights of Menda and Santa Marta. The distance from Coroico in Bolivia to Huanuco is 680 miles, from Huanuco to Loxa 500, from Loxa to Riobamba 180 miles, giving a distance from Coroico to Riobamba of 1200 miles.⁶⁵

IV. COLLECTION, PREPARATION, AND COMMERCE OF THE BARK

Cascara is a Spanish word meaning "bark"; the diminutive, *cascarilla*, signifies a thin bark, and was used as a general term for cinchona bark. A *cascarillero*, then, is a bark-cutter or stripper; the word was sometimes applied to any one concerned in the collection and preparation of the bark for the market, but in a more specific sense it was used for those who engaged in the actual labor of taking the bark from the tree; these were usually Indians.

The methods employed in stripping the bark appear to have varied in different localities and perhaps at various times. The trees were either left standing or were cut down. Of the stripping of the standing tree we have an account in a paper communicated to the Royal Society in 1737 by Dr. John Gray, who had received it from William Arrot, a Scotch surgeon resident in South America. Arrot says:—⁶⁶

⁶⁵ Weddell, *l. c.*, p. 26; Markham, *l. c.* p. 21.

⁶⁶ Gray, J. An account of the Peruvian or Jesuits' bark, from some papers by Mr. William Arrot. Roy. Soc. London, Phil. Trans. Abridged 1737. London 1809, p. 142.

The properest season for cutting the bark is from September to November, the only time in the whole year of some intermission from rain in the mountains. Having discovered a spot where the trees most abound, they first build huts for the workmen, and then a large hut to receive the bark to preserve it from the wet; but they let it lie there as short a time as possible, having beforehand cut a road from the place where the trees grow, through the woods, sometimes three or four leagues to the nearest plantation or farm-house in the low country, whither, if the rain permits, they presently carry the bark to dry. These preparations made, they provide each Indian, these being the cutters, with a large knife, and a bag that can hold about 50 lbs. of green bark; every two Indians take one tree, whence they cut or slice down the bark, as far as they can reach from the ground; they then take sticks about half a yard long each, which they tie to the tree with tough withs, at proper distances, like the steps of a ladder, always slicing off the bark, as far as they can reach, before they fix a new step; and thus they mount to the top, the Indian below gathering what the other cuts; this they do by turns, and go from tree to tree, till their bag is full; which, when they have plenty of trees, is generally a day's work for one Indian. As much care as possible must be taken that the bark is not cut wet; should it happen, it is to be carried directly down to the low country to dry, otherwise it loses its color, turns black, and rots; and if it lie any time in the hut without being spread, it runs the same risk: so that while the Indians are cutting, the mules, if the weather permits, ought to be carrying it down to the place appointed for drying it, which is done by spreading it in the open air and frequently turning it.

This practice was that of the Loxa forests, of which La Condamine gives a similar account.

In the regions explored by Weddell the practice was different, the trees being cut down before the stripping began. He gives a detailed account of it in the first part of his '*Histoire Naturelle des Quinquinas*':—

The name *Cascarilleros* is given to the men who cut the bark, and is sometimes extended to those who engage in its commerce. The bark-strippers are for the most part men who have been engaged in this severe operation from their childhood, and are accustomed to guide themselves by instinct, so to speak, in the forests. With no other compass than this intelligence peculiar to the man of nature, they made their way through these inextricable labyrinths as if the horizon lay before them. Often has it happened to men less experienced to lose themselves in the forests never to be seen again.

The only season not adapted to cutting the bark is that of the rains, which last about as long as a French winter. Although some persons assert that the time of the ascent of the sap is the proper one for attacking the tree, their counsels are not followed in practice; and exception is made of the rainy season only because of the physical discomfort which it brings upon the men.

The strippers do not go in search of the tree on their own account, but are engaged in the service of some trader or small company, and a man of confidence is sent to the forest with them with the title of *Mayordomo*; this *Mayordomo* is charged with the reception and examination of the barks which are brought to him from various parts of the forests and he has, besides, the charge of the provisions and their distribution.

The first care is to make a preliminary survey, employing experienced *cas-carilleros*, the *diestros* or *practicos*. The business of these *diestros* is to penetrate into the forest in various directions and to ascertain up to what point it may be expedient to carry the exploitation. They must determine the presence and ascertain the relative number of cinchona trees as well as the direction and situation in which they are found; and they must bring back specimens by which the quality of the bark can be estimated.

The first survey is the most delicate part of the operation, for it demands much experience and sagacity and it is upon its results that the success of the enterprise depends. If the report of the *diestros* is favorable, a path is cleared to a place which is to serve as the basis of operations, and from this moment the part of the forest which is commanded by the new road becomes the property of the undertaker and no other *cas-carillero* is permitted to work there.

As soon as the *mayordomo* arrives with his strippers, he chooses a spot favorable for the pitching of the camp, as near as possible to a spring of water or a river. He constructs a shed for the storing of the provisions and the bark, and if he foresees that the stay will be long, even sows grain and some vegetables. Experience has shown that one of the elements of success consists in the workers' having an abundant supply of provisions. In the meantime the *cas-carilleros* are scattered through the forests singly or in small bands, each one carrying wrapped in his *poncho* and slung on the back provisions for several days and his bedding for the night.

The cinchonas rarely compose extensive forests, but occur in groups scattered here and there. The Peruvians call these groups *manchas*; sometimes, but this is rare, the trees occur singly. However, this may be, it is to their discovery that the *cas-carillero* bends all his skill; it is by the slightest indications that he recognizes the object of his search; the smallest glint of light peculiar to the leaves of a species, the particular color of the leaves, the peculiar character of a mass of inflorescence—all these things enable him to recognize a cinchona tree at a distance. In other circumstances he is confined to the appearance of the outer layers of the bark, the *enves*, as they are called, which present peculiar characters. Often dead leaves which he may encounter on the ground indicate the neighborhood of cinchonas, and if they have been swept to the spot where he finds them by the wind, he knows from what direction they have been blown.

To strip the bark, the tree is cut down with an axe, the point at which the chopping takes place being stripped of the bark in order that none may be lost; and as the thickest part of the tree and hence the most profitable is near the base, it is customary to dig around it in order that the decortication may be as complete as possible. It is rare that the tree falls immediately after it has been cut to a sufficient depth, as it is held up by climbing plants and neighboring trees.

When the tree is finally down, the outer, dead bark is beaten off with a club, wooden mallet, or the back of the axe, and the live bark thus laid bare, which is often cleaned with a brush. This bark is then cut through its entire thickness by uniform incisions to indicate the sheets or plates that are desired and separated from the wood by an ordinary knife or other similar instrument, with the end of which the wood is also scraped. If the position in which the trunk lies makes it impossible to strip all the bark in this first operation it is cut into pieces in order that these may be turned. The dimensions of the strips to be cut off depend upon circumstances; however, for facility in transportation and prepa-

ration the pieces are usually four to five decimetres long and eight to ten centimetres wide. The bark of the branches is stripped in the same way as is that of the trunk, with the exception that it is not first beaten, custom demanding that it appear in the market with the outer layer remaining.

The drying of the bark also varies in the two cases. The smallest sheets of the bark of the branches or of small trunks, destined to form the quilled bark or *canuto*, are simply exposed to the sun, whereby they roll up into cylindrical pieces. Those sheets which come from the large trunks and which are to form the flat cinchona, *tabla* or *plancha*, are subjected to pressure while drying in order to prevent their rolling up; to this end, after a preliminary exposure to the sun, they are piled up in the form of crossed squares, some heavy objects being then placed upon the pile. The next day the sheets are again exposed to the sun for some time, again subjected to pressure, and so on, the final drying being effected under pressure.

The method of preparing the bark for the market as described is the one most commonly used, but the practice undergoes various modifications according to the locality and the character of the tree. In many places the bark is not pressed or pressed imperfectly, so that the pieces twist and roll up. The outer, dead bark is often incompletely removed or merely scraped. Often, also, probably in order to increase the weight, a quantity of moisture is allowed to remain, but this is apt to lead to deterioration of the bark. It therefore happens that certain barks which would be identical in appearance if prepared in the same way exhibit quite different characteristics depending upon the method employed.

Finally, the packing of the bark for the market:—This is the care of the *mayordomo*. As the strippers bring in the barks, he submits them to a kind of garbling, rejecting those of inferior quality, submitting the better kinds to further drying if necessary and forming them into parcels of about equal weight, which are sewed in large sheets of canvas. Thus prepared the bundles are transported on men's backs or on asses or mules to the entrepôts, where they are usually covered with an envelope of fresh leather which, upon drying, becomes very dense. In this form they are known as *seruns*, or *seroons*, and it is in this form that they arrive in Europe. The usual weight of a seroon is 70 to 80 kilograms but is sometimes less.⁶⁷

The life of the *cascarillero* was one of perils; there was always the danger of going astray in the woods and becoming lost, and there was the risk of losing one's provision by some accident when the strippers went far from the camp. Weddell himself relates a case in point:—On one occasion while ascending the Coroico he landed on a beach whose pleasant shade invited him to spend the night there. Making an inspection of the surroundings, he found nearby the hut of a *cascarillero* and not far from it, stretched on the ground, the body of a man in the throes of death. The body was nearly naked and presented a horrible aspect, the face being so swollen as to be hardly recognizable as that of a

⁶⁷ Weddell, *l. c.*, p. 8.

human being, the limbs in a frightful condition, and the entire body covered with swarming insects. On the roof of the hut Weddell found the remains of the man's clothing, a straw hat, some rags, a knife, and an earthen pot containing the remains of his last meal. He had undoubtedly succumbed to starvation and the stings of the insects helped to bring about his end.

Till the year 1772 all the cinchona bark which reached Europe was collected in the forests of Loxa, Ayavaca, and Jaen de Bracamoros, that is to say between the third and fifth degrees of South latitude, and up to 1775 Loxa bark was the only kind to be found in commerce. The trade became so extensive and the bark was in such high repute that it was necessary for good barks to be recommended by a certificate of their origin sworn to before a notary.⁶⁸ In Payta, the nearest port, the examination of bark for adulterations was early established, although, according to the testimony of La Condamine, it was not always efficient. In consequence of the discoveries in the north, the barks of New Granada came into notice; commerce in those barks began and soon reached great dimensions, the barks being exported from Cartagena and Santa Martha. The English and North Americans opened a contraband trade with these ports, which enabled them to undersell the Spanish merchants who received their supplies by the long route around Cape Horn. The markets of Europe were soon as abundantly supplied with the New Granada barks as they were with those of Loxa. The discoveries of Francisco Renquifo in the south of Peru, where he found the *Cinchona nitida*, led to the opening of the commerce in the true Peruvian barks in 1776, and the expedition of Ruiz and Pavon at about the same time revealed other sources in the same district. An enterprising man, Don Manuel Alcarraz, brought the first specimens of these barks to Lima, made the inhabitants aware of their value, and thus gave the first incentive to the establishment of the trade. Then, from time to time, medicinal cinchona barks were discovered in the northernmost and southernmost regions, in the mountains about Santa Martha, and in the Kingdoms of Buenos Ayres, at La Paz and Cochabamba, where an officer of marine, Rubin de Celis, and the German botanist, Thaddaeus Haenke, pointed out their valuable febrifuge properties.

⁶⁸ La Condamine, *l. c.*, p. 2.

Since the year 1780 Europe received barks from the ports of Payta, Guayaquil, Lima, Buenos Ayres, Cartagena, and Santa Martha, the barks going partly to Spain and partly, by smuggling, directly to England and North America. But all these barks were not true cinchona barks, and many of the true cinchonas were of inferior quality and even worthless—because species were stripped which were low or wanting in alkaloids. Dealers were therefore under the necessity of drawing distinctions, and they divided the barks into two classes, the *true* and the *false* cinchonas, a rough classification which led to great confusion when attempts were made to attribute them to their respective sources, geographical and botanical. "Without considering," remarks Humboldt⁶⁹, "that true fever barks have the same medicinal action but display it in varying degrees, the dealers separated cinchona barks into *true* and *false*. Cinchona barks of the Loxa kind were demanded without considering that already since 1738 three to four different kinds had come from Loxa to Europe, which barks had been obtained from quite different species of *Cinchona*. It was forgotten that the value of the bark depended upon the locality in which the parent tree grew, the age of the tree, whether the bark was dried quickly or slowly. Barks of the same species were not recognized as such, according as they came in thin rolls *canutillos*, or thick *cortizones*, or in the powdered form. Soon, either accidentally or by design, barks of *Wintera granadensis* and certain tanniferous *Weinmannias* were mixed with cinchona; indeed barks were often colored by an infusion of Brazil wood." Humboldt states further that certain West Indian barks, supposed to be *Cinchona*, were mixed with the true South American barks; and, again, other barks with febrifuge properties were called *Cinchona*, though they did not belong to that genus; thus in the commercial circles of Cadiz, *cascarilla* or *quina de Cumana* and *quina de Angostura* were quoted though they were not cinchonas.

With the discovery of the barks of New Granada and southern Peru the monopoly of the bark at Loxa was broken, and intense commercial rivalry ensued, leading to strange practices. "Some of the queerest trade tricks arose," says Humboldt,⁷⁰ "Certain

⁶⁹ Humboldt, l. c., p. 91.

⁷⁰ *Ibid.*, p. 67.

commercial houses in Spain, which for half a century had enjoyed the monopoly of the trade in Loxa bark, sought to bring discredit upon those of New Granada and southern Peru. They found complacent botanists who, by raising varieties to the rank of species, attempted to prove that the Peruvian cinchonas were specifically different from those growing about Santa Fé. Geographers even declared that it was impossible for medicinal cinchonas to grow beyond a given latitude in the northern hemisphere. Since, in the meantime, the trade in the cinchonas of Huamalies and Huanuco, which Ortega, Ruiz, Pavon, and Ta-falla commended, soon fell into the hands of those who had been engaged in the South Pacific trade with the old cinchona barks of Loxa, the new Peruvian barks gained access to Spain more readily than did those of Santa Fé. The latter, which the North Americans and English managed to import from Cartagena, enjoyed a pre-eminent reputation in England, Germany, and France. The activity of rival merchants went so far that in Cadiz a stock of the best orange-colored bark of New Granada which Mutis had had stripped by royal command was burned as worthless at the very time that the Spanish field-hospitals were suffering from an inadequate supply of this valuable remedy. A portion of the bark which had been condemned to the flames was surreptitiously purchased by English merchants at Cadiz and auctioned off in London where it fetched high prices."

Humboldt's statement is possibly exaggerated. He was always strongly influenced by his partiality for Mutis which he shared with the New Granada barks. The fact is that it was subsequently admitted that the Cartagena barks were in every respect inferior to those derived from the ports of the Pacific, and they eventually disappeared from the market. It is probable that the barks destroyed at Cadiz were worthless as a febrifuge and deserved their fate. Up to about 1830 American druggists, because of the trade restrictions imposed upon the exportation of the bark in South America, derived their supplies from London; but when the commerce of South America was freely opened to the United States, they were able to supply themselves directly from the sources.

The discovery of quinine in 1820 led to an enormous increase in

the demand for the bark of *Cinchona Calisaya*, the product of the Bolivian forests. The drain upon the forests became so great that in a short time hardly a tree was left in the vicinity of the inhabited places. No attempt was made to meet the situation until 1830, when, under the administration of General Santa-Cruz, the Bolivian government found it necessary to take measures to check the rapid exhaustion of the cinchona forests; the government conceived the idea of prohibiting free trade in the bark and limiting the exportation, and in 1834 issued a decree to that effect, but made no effort to enforce it. Matters thus went on as before, until later a decree prohibited the felling of the trees for five years, but before the expiration of that period the law was repealed, and an attempt was made to limit the export by imposing upon the bark an export duty of twenty dollars the quintal. In 1841 General Bolivian was elected to the presidency, but he made no important changes in the laws regulating the cutting and exportation of bark; in 1844 the congress authorized him to negotiate the capital necessary for the establishment of a national bank to purchase and export all the bark shipped in the state at a fixed rate proportionate to the bank's capital. The capital necessary for this operation not being forthcoming, the government then asked for bids for the exclusive exportation of the bark, but no offers were made and this scheme fell through. Then, in 1845, the plans were somewhat modified, and the firm of Dr. Jorge Tesanos Pinto and Co. was granted by the Government a monopoly for five years, the payment for the privilege being 119,000 dollars; it was stipulated that not more than 4000 quintals (a quintal = a hundredweight) of bark were to be exported annually. In order to make as high profits as possible the firm paid the *cascarilleros* such low wages that great dissatisfaction ensued, and the monopoly was revoked in 1849.

Free trade for one year, with an export duty of twenty dollars the quintal, was thereupon re-established, with as little success as before, and in 1850 the government again had recourse to the monopolistic system,⁷¹ the favored firm being that of Aramayo Brothers & Co. The new company began operations April 1, 1850. It was to pay the government an annual sum of 142,000

⁷¹ Pharm. Jour. XI, p. 215, 218.

piastres for the right of exporting annually 7000 quintals of bark, purchasing from the *cascarilleros* the *tabla* at sixty dollars and the *canuto* or quill bark at thirty to thirty-six dollars the quintal. The Pinto Company had paid only eighteen to twenty-two dollars per quintal for the *tabla* and eight to ten for the *canuto*; the new management was therefore a very advantageous one for the *cascarilleros*. The consequence was that the *cascarilleros* brought in such large quantities of bark that at the end of the first year there arrived at La Paz more than 20,000 quintals of cinchona bark, more than the Pinto company had exported in five years. This result led the Government to take action again; it decreed that all the cinchona bark stripped in the forests should be deposited in the warehouse of the Aramayo Company and that no more bark should be stripped for a period of four years. The first of these measures was designed to prevent contraband trade, and was decidedly in favor of the monopoly. The second was a blow for the *cascarilleros*. The bark-collectors were naturally discontented, and so great an outcry arose that in 1851 the congress voted that the executive had gone beyond his powers when he made this arrangement with the Aramayo Company, and declared it null and void. At that time the Aramayo Company had purchased 14,000 quintals of the bark and had proposed to buy 14,000 more (composing the stipulated supply for the next two years), paying one-third the price in ready money and giving notes for the rest. Many of the merchants opposed this, and another company, Pedro Blaye and Co., was formed, engaging to buy all the bark then for sale, whether at La Paz or Cochabamba, as well as that which should be brought from the forests before the end of 1851. It was now feared that the market would be overstocked and that both companies would find themselves in difficulties; indeed, the Blaye Company failed after two years. The Government then decided to undertake the exportation of the bark which was still in the warehouses. In 1858 a decree was issued to abolish the monopoly; measures were taken to regulate the transition from the system of monopoly to that of free trade; and in 1859 Dr. Linares, the president, declared the stripping of bark in the forests to be free and reduced the duty twenty-five per cent on the current prices, to be fixed at the beginning of each year.

Weddell states that in the two years which had preceded the failure of the Blaye Company, the forests of Bolivia alone had produced more than three million pounds of cinchona bark, the result of the sudden rise in price which had taken place after the fall of the Pinto Company. He also gives a picture of the tremendous waste of bark which attended the stripping of the bark during the "boom." As has been stated, the *tabla*, the large bark obtained from the trunk of the trees, fetched 60 piastres the quintal, and the *canuto*, the thinner and smaller barks from the branches and upper parts of the tree, about half as much. The result was that in many places the tree was not cut down and the parts of the bark, the thin, which were not easily reached, were left on the tree, only the thicker part being removed. He was told that this was the general practice in the cinchona forests which had recently been found at Cochabamba; and even when the tree was cut down that part of the bark which lay on the under side was left in place in order to save the trouble of turning the tree. Regarding the unstable policy of the Bolivian government with respect to the commerce in cinchona, Markham observes:—

This Bolivian legislation on the cinchona bark, which is considered with justice the most important product of their country, is very curious, and sufficiently demonstrates the futility of attempting a system of protection and monopoly. Instead of taking measures to prevent the reckless destruction of the trees, to establish extensive nurseries for young plants and thus ensure a constant and sufficient supply of bark, these Bolivians have meddled with the trade, attempted to regulate European prices by the most barbarous legislation and allowed the forests to be denuded of cinchona trees.⁷²

V. INTRODUCTION OF CINCHONA TREES INTO JAVA AND INDIA

The rapid and reckless destruction of the cinchona forests of South America became a matter for serious consideration on the part of European quinologists and drug-merchants about the middle of the nineteenth century. It is strange that it should not have caused disquietude long before this, for earlier warnings were not wanting. Already La Condamine had expressed concern, and as early as 1735 Ulloa reported to the Spanish Government that the custom of cutting down the trees without planting

⁷² Markham, *l. c.*, p. 59.

others in their place would undoubtedly cause their extirpation. "Though the trees are numerous," he says, "they have an end," and he suggested that the Corregidor of Loxa should be directed to appoint a commissioner whose duty it would be to inspect the forests and see that in place of every tree stripped a new one be planted, under pain of a fine.⁷³ Nothing was done, however, and sixty years afterward Humboldt reported that 25,000 trees were destroyed in one year. It is said that the Jesuits inculcated it as a religious duty to set out cinchona plants for every tree destroyed; if this be true, their admonitions were without effect. In 1792 Ruiz complained of the extravagant practices of the exploiters and suggested the idea of cultivating cinchona out of its native regions. To end the state of affairs, Mutis suggested that the Spanish Government be advised to limit the export of the bark, hoping to achieve something in this way. Fée, of Strasbourg, in 1824, urged cultivation in South America, and in 1839 Royle pointed out that the Nilgiri Hills, in India, might furnish suitable localities for the cultivation of cinchona, and a similar suggestion with respect to Java was made in 1837 by Fritze, director of medical affairs in that island; it appears that Reinwardt had called the attention of the Dutch Government to the matter as early as 1829. Poeppig also raised a warning voice. Weddell was seriously concerned when he became aware of the depredations in the *Calisaya* forests of Bolivia. He wrote:

Those who believe that the forests are restoring themselves from seeds and from the branches which spring from the remains of the trunk left in the ground, are not altogether wrong. Too often, however, the stump dies and those parts that are left alive grow slowly, and if they attain to a certain degree of development are sacrificed to the axe. A watch exercised over the exploiters by means of inspectors would prevent the rapid deforestation in a measure; but it is a different matter to watch over a forest in France and one in the New World, particularly when the latter extends over a space of twenty thousand leagues. It seems to me that there are only two methods for preventing the too rapid exhaustion of the cinchona forests; one is to limit the exportation to a degree commensurate with the productive capacity of the forests; the other to put plants under cultivation. The limitation of exportation would perhaps be the surer method; but it is to be feared that the ratio between consumption and production is already such that it would be impossible to establish the balance. There remains, then, the question of cultivation. If it is a tree that can be acclimated in any of the French colonies, it would be worth trying.⁷⁴

⁷³ Markham, *l. c.*, p. 70.

⁷⁴ Weddell, *l. c.* p. 13.

Markham, too, was very positive in urging the necessity of action. He found the only solution to lie in the cultivation of the tree in suitable regions outside of South America; referring to the reckless methods employed in stripping, he wrote:

But where the trees are felled, it is only necessary to observe the precaution of hewing the stem as near as possible to the root in order to be sure of its after-growth. Under these circumstances, after six years, the young trees are ready to be felled again in the milder regions, and after twenty years in cold and exposed localities. From the base of the stems, when not barked, a number of shoots spring out between the bark and wood; and Dr. Karsten says that, though an interval of rest of twelve or fifteen years must be given to the forests where the cinchona trees have thus been felled, this only promotes further investigation in the endless untrodden forests, while, in the meantime, the younger generation is growing up in those which have already been exhausted.

The danger, therefore, is not in the actual annihilation of the cinchona trees in South America but lest, with the increasing demand, there should be long intervals of time during which the supply would cease, owing to the forests being exhausted and requiring periods of rest. In many districts this is already the case. The bark which comes from Loxa is in the minutest quills, and in the forests of Carabaya, after an interval of rest of several years, the root-shoots had scarcely grown to a sufficient size to yield anything but quill bark. Then again the supplies of bark from South America are not nearly sufficient to meet the demand, and the price is kept so high as to place this inestimable remedy beyond the means of millions of natives of fever-visited regions. For these reasons the incalculable importance of introducing the cinchona plant into other countries adapted for its growth, and thus escaping from entire dependence on the South American forests, has long occupied the attention of scientific men in Europe.⁷⁵

The Dutch were the first to take active steps to introduce the cinchona trees into the eastern hemisphere. Java was considered as the country which fulfilled the conditions as to climate, altitude, and so forth; and in 1852 Mr. Pahud, then Dutch Minister of Colonies, received authorization to employ an agent to collect plants and seeds of valuable species in Peru and bring them to Java. His choice fell upon Mr. Justus Charles Hasskarl, superintendent of the gardens in Java. Hasskarl sailed for Peru in December, 1852. He was ordered to collect plants and seeds of as many kinds of cinchona species as possible and not to confine himself to the *Cinchona Calisaya*.

Proceeding from Lima to Tarma, Hasskarl crossed the Andes, descended the eastern slope into the regions about Vitoc, Uchubamba, and Monobamba, and thence returned to the higher

⁷⁵ Markham, l. c., p. 71.

altitudes of the Andes. He found a species which he thought was *Cinchona ovata*, of which he collected a quantity of seeds, as also seeds of *Cinchona pubescens* and *Cinchona amygdalifolia*. At a place called Escalera de San Rafael, on the road between Uchubamba and Xauxa, he collected specimens of *Cinchona lanceolata* Pavon. He next went to Cuzco and from there to Sandia, in the province of Carabaya; but he arrived too late to obtain seeds of the cinchona, which obliged him to take up his residence in Arequipa until the following year. In March, 1854, he again crossed the Andes, at Puno, wandered over a part of Bolivia, and at length reached the village of Sina in Carabaya in April. A request to the governor, Don Juan de la Cruz Gironda, for specimens and seeds, was refused, but the governor introduced him to a man named Henriquez, an adventurous and somewhat unscrupulous spirit who promised to secure for him four hundred plants of *Cinchona Calisaya*. Hasskarl had taken an assumed name in order to allay the mistrust of the inhabitants who were jealous of their monopoly in the bark. While awaiting the arrival of the promised plants he resided in Sandia, wisely abstaining from entering the forests. Henriquez faithfully redeemed his promise, and Hasskarl left Sandia with his plants in June, 1854. He finally sailed from Peru on August 27, arriving at Batavia in December with twenty Wardian cases; all his plants, except two, afterward died. Hasskarl was intrusted with the cultivation of cinchona plants in Java with the rank of assistant resident, and was made a knight of the Netherlands Lion and commander of the Order of the Oaken Crown.

The species called by Hasskarl, *Cinchona ovata*, at first formed the greater part of the cinchona cultivated in Java. It was found, however, that Hasskarl had been mistaken in assigning it to that species; it was in fact a new one, and was named *Cinchona Pahudiana*, in honor of the Minister of Colonies. A plant of *Cinchona Calisaya* which had been raised in Paris from seeds sent home by Dr. Weddell, a number of plants from seeds previously sent from Peru, and seeds of *Cinchona lancifolia* sent by Dr. Karsten from Colombia, in addition to those brought by Hasskarl, formed the first experimental cinchona plantation in Java. The site for the first plantation was selected by Hasskarl and his

associate, Teysmann, at Tjibodas, thirty miles south of Batavia, on the northern slopes of the range, which crosses Java from east to west and at an elevation of 4400 feet above the sea. Ground was also prepared at Tjipannas, half a mile from Tjibodas and 4700 feet above sea level. But the ground was unsuitable, being too shallow, and the sites were in too low and warm a climate. By the end of 1855 it became evident that the experiment was a failure. Dr. Franz Junghuhn came to Java in December, 1855, with 139 cinchona plants which had been raised from seeds in Holland, but seventy-six of these were dead at the end of six months. In June, 1856, Hasskarl was relieved of his duties, and Dr. Junghuhn was appointed in his place. Dr. J. E. de Vry, a chemist, was sent to Java charged with the duty of making chemical analyses of the cinchona barks.

Dr. Junghuhn found the situation to be anything but encouraging. Of the 139 cinchona plants which he himself had brought, only 63 were growing; three sickly plants represented the seeds of *Cinchona lancifolia*; three plants also were all that remained of the *Cinchona Calisaya* brought from Peru by Hasskarl; the remainder consisted of the species collected by Hasskarl in Uchibamba; the whole made a total of 300 plants. Junghuhn saw the necessity of introducing a new system, which he did in 1856. He transplanted the trees from Tjibodas to the Malawar Mountains, on a site more suitable to their development. In 1857 plants both of *Cinchona Calisaya* and of the northern species were in blossom, and they bore fruit in 1858. The experiment promised to be a success, and so it turned out to be; on December 31, 1860, the number of cinchona plants growing in Java was: *Cinchona Calisaya*, 7316 plants and 1030 cuttings; *Cinchona lancifolia*, 80 plants and 28 cuttings; *Cinchona Pahudiana*, 939,809 plants and 18 cuttings;—the total number of plants, 947,205. There were, besides, 700,264 seeds in stock or sown. The highest of the *Calisayas* had attained 15 feet, and the *Cinchona Pahudiana* 28 feet. One of the trees of *Cinchona lancifolia* had grown to a height of 15 feet. Dr. de Vry found that the results with *Cinchona Calisaya* were successful; in August, 1860, he obtained 5 per cent of alkaloids from the bark of a trunk six years old and 2½ per cent from the branches. The species introduced by Hasskarl

did not yield satisfactory results; up to 1860 Dr. de Vry had obtained only 0.4 per cent alkaloids from the *Cinchona Calisaya*, an analysis which was confirmed by Mr. Howard. Both declared it an inferior species. This was unfortunate, for the species was a hardy one, and as it required less care than the others, it had been extensively propagated. Dr. Junghuhn published two reports on the cultivation of cinchona in Java in 'Bonplandia'⁷⁶ the first appearing in the number for March, 1858, and the second in the numbers for July and August, 1860. Markham had these translated and circulated among those who were interested in the cultivation of cinchona in India and Ceylon.

At the same time that the Dutch were conducting their experiments in Java, the attention of the British Government was directed to the feasibility of introducing the cultivation of cinchona trees into India. A spur was given by Royle who, in 1852, in a report addressed to the East India Company, pointed out that the Government of India was then spending more than 7,000 pounds a year for cinchona bark in addition to about 25,000 pounds for quinine. Efforts were made on the part of the British Government to obtain plants and seeds through the intervention of the British Consuls in South America, but these were unsuccessful. Mr. Cope, indeed, the Consul-General at Quito, sent a box of cinchona plants and seeds from Cuenca and Loxa, but they did not long survive their extended journey. Seeds of *Cinchona Calisaya* were sent to the botanical gardens at Calcutta, but they failed to germinate. In 1853 six plants of the same species which had been raised from seeds sent home by Weddell were contributed by the Horticultural Societies of Edinburgh and London, but, though they arrived in good condition, they soon died from careless handling. These abortive attempts led Royle to draw up a second report on the subject in May, 1853, but the matter rested until March, 1856, when Royle made another effort to induce the East India Company to secure cinchona plants and seeds from South America for cultivation in India. Dr. Royle's death in 1857 again put an end to the discussion until, in 1859, energetic measures were adopted which finally ended in complete success. Sir, then Mr., Clements R. Markham gave the matter close atten-

⁷⁶ Bonplandia, VI, 1858, p. 70; VIII, 1860, p. 206, 227.

tion and finally offered his services, which were accepted. The name of Clements R. Markham is illustrious in more than one department of science. Already while still a schoolboy he had become deeply interested in natural science, and especially in geography, which was with him a veritable passion that endured all his life. He was especially fit for the task which he undertook at this juncture. He had already made extensive archaeological explorations in South America, he knew the country, he spoke fluently both the Spanish and Quichua languages; and he was animated by a rare zeal and forethought. He was well aware of the difficulties of the undertaking in which he had pledged himself to engage, and he devoted careful study to even the minutest details so necessary to insure its success.

Markham pointed out the desirableness of procuring by different collectors all the more valuable species instead of confining the operations to one district. He writes:

This would entail the despatch of five agents: to Bolivia or Carabaya for the Calisaya plants; to Huanuco in Peru for the gray barks; to Loxa in Ecuador for the crown barks; to Huaranda in Ecuador for the red barks; and to Popayan for the Colombian barks. These five agents were to work simultaneously under my general superintendence and a special steamer was to be supplied to convey the collection of plants and seeds from the five ports of Islay, Callao, Payta, Guayaquil, and Buenaventura, direct to India across the Pacific Ocean. If the scheme failed at one or more points—which, considering the enormous difficulties was quite probable—my plan was to repeat the work in the next season, and if necessary in the next, and the next until complete success was secured.

I was fully determined that the whole plan should, sooner or later, be carried out. If it had been adopted in its entirety, as I recommended, the undertaking would have been completed in a quarter of the time and at a tenth of the expense. But the delay in obtaining consideration for my plans prevented me from maturing them fully before leaving England. I received sanction for the expeditions into the Calisaya and red bark regions in good time and made all the necessary arrangements. But I failed to obtain any answer to my proposals for the Huanuco and Colombian regions, which I submitted on May 13, 1859, until the end of the following September; and instead of steps being taken to furnish me with a steamer, I was only authorized to charter a sailing vessel myself, if I could find one on the west coast of South America. Subsequently, in a letter dated May 17, 1860, I was empowered to charter a steamer, but this letter never reached me until after my arrival in India. In point of fact, there was no steamer available on the west coast of South America at that time; and it was necessary that the Government should make arrangements for the conveyance of the plants and seeds to India. This was not done, although H. M. S. *Vixen* was at Callao and about to go home, and she might have perfectly taken the precious cargo to India, direct, thus ensuring its safe transit. The alternative was a

most perilous and roundabout series of voyages involving four transshipments and great changes of climate, by Panama to England, and then by Egypt to India. Such a journey made success, as regards the plants, very precarious and doubtful, and the loss of a large percentage almost certain. There would be less chance of loss in the transmission of seeds.⁷⁷

In assigning the various regions to the various agents who were to collect the young plants and seeds, Markham chose for himself the borderlands of Peru and Bolivia, where he proposed to obtain the *Cinchona Calisaya*. He selected as assistant an intelligent and experienced gardener named John Weir, who had been highly recommended to him. Markham reserved this region for himself because the work there was surrounded by special difficulties, and it was important that he should collect information regarding the climate and soil of this very valuable tree.

For the collection in the forests of Ecuador in which grew the *Cinchona succirubra*, which furnished the red bark, Markham was so fortunate as to secure the services of Richard Spruce, the eminent botanist and explorer, who for ten years had been engaged in collecting and studying the vegetation of the Amazon valley including the Rio Negro, and bringing together a huge mass of valuable geographical information. Spruce was in the position to furnish an accurate botanical description of the *Cinchona succirubra*, which had been wanting up to that time, and to give a scientific account of the forests where it grows. To him was assigned a capable Scotch gardener named Robert Cross, who had been recommended by Sir William Hooker. Cross joined Dr. Spruce in Ecuador. Mr. Pritchett, who had spent some time in South America and was well acquainted with the Huanuco forests, was assigned that region. This completed Markham's arrangements for the first year, in which he hoped to complete the work in three out of the five cinchona regions.

Markham started from Islay in March, 1860, arriving in the middle of May, by way of Arequipa at Curcero, the province of the capital of Carabaya. Proceeding to Sandia, he met with the first cinchonas in the form of the shrubby variety of *Cinchona Calisaya* called *Josephi*ana. Later he found the better varieties, as also *Cinchona ovata* Ruiz and Pavon, *Cinchona micrantha* Ruiz and Pavon, and *Cinchona pubescens* Vahl. He collected plants of

⁷⁷ Markham, *l. c.*, p. 93.

all these sorts, but chiefly of the first three, shipping 564 of them at Islay in June, 1860. Markham's plan to prosecute his work in Bolivia was frustrated. Many difficulties were in the way. In the first place, the exportation of plants and seeds of cinchona from Bolivia was prohibited by law, under heavy penalties, as a considerable part of the revenue of the state was derived from the bark trade. Then again, there was the prospect of war between Bolivia and Peru, and troops were massed at various points. In the event of war Markham's mules, had he gone into Bolivia, would have been seized. War did not take place, but Linares, the president of Bolivia, issued a decree prohibiting all traffic or the passage of travellers from one hostile country to the other, a decree which was strictly enforced and which would have made it impossible for Markham to have conveyed himself and his companions, with laden mules, from Bolivia to the coast. Considering these difficulties, he abandoned his idea of penetrating into the Bolivian forests and confined his operations to the cinchona forests of the Peruvian province of Carabaya, where similar obstacles did not exist.⁷³ Dr. Spruce's expedition was attended with many difficulties and much danger, but it was in the end successful. Pritchett, also, accomplished his task, and he brought to Southampton six cases containing plants of *Cinchona micrantha* and *Cinchona nitida*, besides a large supply of seed. Some important supplies of plants and seeds were also obtained from the Dutch plantations in Java. Dr. Karsten obtained for British India seeds of *Cinchona lancifolia*, the tree which furnished the valuable bark of New Granada.

The India Government was more circumstantial than the Dutch had been in selecting a site for the cinchona plantations. Meteorological and geological observations were made in order to determine what localities would be best adapted for the cultivation of the trees. It was resolved to undertake the first experiment at certain places in the Neilgherry (or Nilgiri) Hills, on the southwest coast of India, in the Madras Presidency. The chief town of this district is Ootacamund (or Utakamand), about 60 miles south of Mysore and at about the same distance from the Indian Ocean. A woody ravine, of 7000 feet altitude was the site of the

⁷³ Markham, *l. c.*, p. 109.

first plantation. Markham pronounced this locality to be analogous, as regards climate and vegetation, to the cinchona-bearing valleys of Carabaya. Other plantations were established in the neighborhood, and so rapidly did the plants propagate that in 1866 there were more than one and a half million of cinchona plants on the Neilgherry Hills, the species growing best there being *Cinchona officinalis*; by 1872 the number was stated to have increased to 2,639,285, the largest trees being about thirty feet in height, with trunks over three feet in girth. There were also cinchona plantations conducted by private interests. Private plantations were established in the coffee-producing districts of Wynaad, and in Coorg, Travancore, and Tinnevely. The Government of India also established plantations in the Himalaya valleys in British Sikkim, where private speculators also made plantings; the species growing best there were reported to be *Cinchona succirubra* and *Cinchona Calisaya*. Cultivation was also undertaken in the Bombay Presidency and in British Burmah. In 1861 the Government formed a plantation in Ceylon, in the mountain region occupying the center of the island, at an elevation of 5000 feet above the sea; and the coffee-planters of Ceylon also took up the work. Plants and seeds of cinchona were distributed among the people of India by the Government with great liberality, and the promotion of the cultivation of the tree among the people received assistance from the same source. The Government was also extremely liberal in furnishing supplies of seeds to other countries.

VI. THE SPECIES

It was not until 1737 that the plant yielding the fever bark became known to naturalists, when La Condamine wrote his account of it, accompanying it by drawings. Linnaeus gave it the name *Cinchona officinalis*, but in his description he united the description of the species discovered by La Condamine with that of the *Cinchona pubescens*, a specimen which had been sent to him from Santa Fé de Bogota. For a number of years the pharmacopoeias recognized this as the only source of the official bark, botanists being ignorant of the existence of other species. In the course of time a plant was discovered in Jamaica, the generic

character of which corresponded with that established by Linnaeus, to which was assigned the name *Cinchona caribaea*. Various parts of the West Indies yielded analogous species; the island of Tongataboo, in the South Pacific, furnished another; Roxburgh reported one on the Coromandel coast of India; and Nee, one in the Philippines.⁷⁹ None of these was a cinchona. Then came the discoveries of Santisteban, Lopez, Mutis, Ruiz and Pavon, Zea, Caldas, and others, of trees in South America, some of which were cinchonas while others were not. Certain botanists added a number of Brazilian plants to the genus, and the southern parts of the United States also contributed to the list. At one time 46 plants were classified in the genus *Cinchona*.

So unwieldy became the catalogue and so many heterogeneous elements did it comprise that botanists soon found it necessary to distribute the species into several groups, each representing a distinct genus. De Candolle made eight of these:—*Cinchona*, *Buena*, *Remijia*, *Exostemma*, *Pinckneya*, *Hymenodictyon*, *Luculia*, and *Danais*. Endlicher separated the species according to the dehiscence of the capsule: those which opened from the base upward he put into the genus *Cinchona*; those which dehisced from apex to base he classified as *Cascarilla*. Klotzsch combined this property of downward dehiscence with the presence of a six-parted corolla and created the genus *Ladenbergia*. The number of species described as *Cinchona* varied with different botanists. Lambert in his 'Illustrations of the Genus *Cinchona*,' published in 1821, admitted nineteen species; De Candolle described sixteen; Lindley admitted twenty-one species besides five which he regarded as doubtful. The subject was in a chaotic condition until Weddell, by his epoch-making investigations, established order.

As was stated in a previous chapter, Humboldt had pointed out that one source of the difficulty lay in the circumstance that the leaves of the same species varied according to the elevations at which the plants grew, the severity or mildness of the climate, the degree of humidity of the soil, and to various conditions surrounding the individual plants and determining their growth. The foliage of the same tree even is diversified in character, and a botanist, inattentive to this fact, might think that he had dis-

⁷⁹ Humboldt, l. c., p. 61, 104.

covered different species from the examination of the leaves of the same branch. The fructification, too, is somewhat variable in character. Taking these facts into account, careful botanists were enabled to fix three characteristics by which a cinchona tree may be known: the presence of curly hairs bordering the laciniae of the corolla, the little pits at the axils of the veins on the under sides of the leaves, and the dehiscence of the capsule from base to apex, although both Karsten and Howard have pointed out that the last is not an absolute indication. Another fact, established by chemical analysis, is that none of the allied genera at one time regarded as *Cinchona* contain any of the medicinal alkaloids. Weddell's characterization of the genus *Cinchona* is as follows:

Calyx: with turbinate tube, connate with the ovary, pubescent; limb superior, five-toothed, persistent; teeth valvate in praefloration.

Corolla: salver-shaped, with a terete or subpentagonal tube; limb five-cleft; the segments lanceolate, valvate in aestivation.

Stamens: five; the filaments inserted in and adnate to the lower tube; anthers linear, inclosed or somewhat exserted at the apex. Ovary crowned with a fleshy disk. Ovules numerous, peltate, in linear placentae, which are affixed on both sides of the dissepiment. Style simple. Stigma bifid, concealed within the tube of the corolla or somewhat exserted.

Capsule: ovate, oblong, or linear-lanceolate, grooved on both sides, crowned by the limb of the calyx, two-celled, many-seeded, septicial, dehiscing from the base to the apex, the valves disjoined, the pedicel split lengthwise. Seeds numerous, affixed in angular-winged, ultimately free placentae. Embryo straight in the axis of fleshy albumin.

Evergreen trees or shrubs growing in the intertropical valleys of the Andes between 10° N. and 19° S. latitude, at from 1200 to 3270 metres (3937 to 10,728 feet) elevation above sea level.

Trunks and branches terete, with a brittle bark rich in quinine, cinchonine, and other alkaloids. Leaves opposite, entire, petioled. Stipules usually free and soon deciduous. Flowers cymose-paniculate, white or usually roseate or purplish, very fragrant.⁸⁰

In 1848 Weddell published in the 'Annales des Sciences Natur-

⁸⁰ Weddell, l. c., p. 17.

elles' a preliminary paper containing his classification of the cinchonas and allied species. This is of great historic interest, and may be reproduced here as it stands:—

CINCHONA LINN.

(DC. *Prod.* IV, 351. exclus spec.)

1. *C. Condaminea*. Humb. et. Bonpl. *Pl. aeq.* I. 33. t. 10 E.
 2. *C. lancifolia*. Mut. mss. ex Humb. in *Mag. Ges. Nat. Berl.* 1807, p. 16.
 3. *C. Calisaya*. Hab. in Bolivia.
 4. *C. amygdalifolia*. Hab. in Bolivia et Peruvia.
 5. *C. Delondriana*. Hab. in Peruvia.
 6. *C. asperifolia*. Hab. in Bolivia.
 7. *C. australis*. Hab. in Bolivia meridionali.
 8. *C. Boliviana*. Hab. in Bolivia.
 9. *C. pubescens*. Vahl in *Act. Havn.* I, p. 19, t. 2.
 10. *C. rufinervis*. Hab. in Peruvia.
 11. *C. Pelletieriana*. Hab. in Bolivia et Peruvia.
 12. *C. affinis*. Hab. in Peruvia.
 13. *C. micrantha*. Ruiz et Pav. *Fl. Peruv.*, 2, p. 52, t. 194.
 14. *C. cordifolia*. Mutis mss. Humb. *Mag. Ges. Nat. Berl.* 1807, p. 117.
 15. *C. purpurascens*. Hab. in Bolivia et Peruvia.
 16. *C. Chomeliana*. Hab. in Bolivia.
 17. *C. Carabayensis*. Hab. in Peruvia.
 18. *C. Humboldtiana*. Lamb. *Monog.*, 1821, p. 7.—*C. villosa* Pav. mss. ex Lamb.
 19. *C. Mutisii*. Lamb. *Monog.*, 1821, p. 9.—*C. microphylla* Mutis mss. ex Zea.—*C. quercifolia* Pav. mss. ex Lamb.
 20. *C. glandulifera*. *Fl. Peruv.*, 3, p. 1, t. 224.
 21. *C. hirsuta*. *Fl. Peruv.* 2, p. 51, t. 192.
- Cinchonae species mihi hucusque non rite cognitae.
- | | |
|--|-------------------------------|
| <i>C. scrobiculata</i> . Humb. et Bonpl. | <i>C. pelalba</i> . Pav. |
| <i>C. nitida</i> . Ruiz et Pav. | <i>C. discolor</i> . Kltzsch. |
| <i>C. ovalifolia</i> . Humb. et Bonpl. | |

CASCARILLA

(*Cinchona* β *Cascarilla* Endlich. *Gen. Plant*, p. 556.)

1. *C. magnifolia*. *Fl. Peruv.* 2, p. 52, t. 196—*Ladenbergia magnifolia* Kltzsch. in *Hayne Arzneigew.*, XIV, adnot. ad t. 15.
2. *C. caduciflora*.—*Cinchona caduciflora* Humb. et Bonpl. *Pl. aequin.* p. 167 in adn.
3. *C. rostrata*. Hab. in Bolivia et Peruvia.
4. *C. heterophylla*. Hab. in Peruvia.
5. *C. acutifolia*.—*Cinchona acutifolia*, Ruiz et Pav. *Fl. Peruv.* 3, p. 1, t. 225.—*Ladenbergia acutifolia* Kltzsch. l. c.
6. *C. nitida*.—*Cinchona nitida* Benth. *Plant. Hartweg.*, p. 190, No. 1048.—*Ladenbergia nitida* Kltzsch. mss. in *Walp. Rep. Bot.* 6, p. 68.
7. *C. citrifolia*. Hab. in Venezuela.
8. *C. Riveroana*, Hab. in Peruvia.
9. *C. Muzonensis*.—*Cinchona Muzonensis* Goudot in *Phil. Mag.* 1828 Febr. p. 132.
10. *C. Pavonii*.—*Cinchona Pavonii* Lamb. *Monog.*, 1821, p. 8.

11. *C. bullata*. Hab. in Peruvia.
12. *C. Carua*. Hab. in Peruvia.
13. *C. Riedeliana*.—*Cinchona Riedeliana* Casaretto, *Atti terz. Riun. Scienz. Ital.* 513.—*Ladenbergia Riedeliana*, Kltzsch mss. in Walp. l. c., 68.
14. *C. Gaudichaudiana*. Hab. in Brasilia.
15. *C. calycina*. Hab. in Nova Granada.
16. *C. undata*.—*Ladenbergia undata* Kltzsch. in Hayne. *Arz.* XIV. adnot. ad t. 15.
17. *C. Roraimae*.—*Cinchona Roraimae* Bth. in Hook. *Journ. Bot.*, III, 214.—*Ladenbergia Roraimae* Kltzsch. l. c.
18. *C. hexandra*.—*Buena hexandra* Pohl. *Pl. bras.*, I, p. 10, t. 8.—*Ladenbergia hexandra* Kltzsch. l. c.
19. *C. oblongifolia*.—*Cinchona oblongifolia* Mut. mss. ex Humb. in *Mag. Ges. Nat. Berl.*, 1807, p. 118.
20. *C. calyptata*.—*Cinchona crassifolia* Pav. *Quin. ined.* ex DC. *Bibl. univ.*, 1829, sc. V. 2, p. 151.
21. *C. macrocarpa*.—*Cinchona macrocarpa* Vahl, *Act. Havn.*, I, p. 20, t. 3, excl. syn.—*Ladenbergia macrocarpa* Kltzsch. l. c.

REMILIA

(DC. Prod. IV, 357)

1. *R. ferruginea* DC. *Prodr.*, IV, p. 357.—*Cinchona ferruginea* St-Hil. *Pl. us. bras.*, p. 1, t. 3.
2. *R. Vellozii* DC. l. c.—*Cinchona Vellozii* St-Hil. l. c., p. 1, no. 2 in adn.
3. *R. Hilarii* DC. l. c.—*Cinchona Remijiana* St-Hil. l. c.
4. *R. paniculata* DC. l. c.
5. *R. firmula*.—*Cinchona firmula* Mart. ex Walp. *Rep.* VI. 67.—*Ladenbergia firmula* Kltzsch. in Hayne, *Arzneigew.* XIV, adnot ad t. 15.
6. *R. densiflora* Bth. in Hook. *Journ. of Bot.*, III, 215.
7. *R. tenuiflora* Bth. l. c., III, 214.
8. *R. Cujabensis*.—*Ladenbergia Cujabensis* Kltzsch. l. c.
9. *R. Lambertiana*.—*Cinchona Lambertiana* Mart. *Linnaea*, VI. *Literbl.* 67.—*Ladenbergia Lambertiana* Kltzsch. l. c.
10. *R. Macrocnemia*.—*Cinchona Macrocnemia* Mart.—*Ladenbergia Macrocnemia* Kltzsch. l. c.
11. *R. Bergeniana*.—*Cinchona Bergeniana* Mart. l. c.—*Ladenbergia Bergeniana* Kltzsch. l. c.

GOMPHOSIA

1. *G. chlorantha*. Hab. in Peruvia.
2. *G. Goudotiana*.—*Cinchona dissimiliflora* Mut. mss. ex Humb. *Mag. etc.* p. 120.—*Exostemma dissimiliflorum* Roem. et Schult. *Syst.* 5, p. 17.—*Ladenbergia dissimiliflora* Kltzsch. l. c.—Goudot. *Collect. Nov. Gran.*, No. 4, bis.

LADENBERGIA

(Kltzsch. in Hayne *Arzneigew.* XIV, adnot. ad t. 15.—Exclus. spec.)

1. *L. dichotoma* Kltzsch. l. c.—*Cinchona dichotoma* Ruiz et Pav. *Fl. Per.*, 2, p. 55, t. 19.

L. Moritziana et *L. Schomburgkii* Kltzsch. mihi imperfecte cognitae.²¹²¹ Weddell, *Ann. Sci. Nat. Bot.* 1848, 3rd. ser., X, pp. 5-14.

In 1870 Weddell published a completely revised and far more detailed classification which included the species yielding the important "red bark," rich in quinine, which had found no place in the list of 1848.²² The classification of 1870 is as follows:—

CINCHONA

I—STIRPS CINCH. OFFICINALIS:—

- | | |
|--------------------------------|---|
| Ramus A. <i>Euofficinales</i> | { <i>C. officinalis</i> .
α <i>Uritusinga</i> .
β <i>Condaminea</i> .
γ <i>Bonplandiana</i> .
* <i>C. crispa</i> . |
| Ramus B. <i>Macrocalycinae</i> | { <i>C. Macrocalyx</i> .
* <i>C. Palton</i> .
* <i>C. suberosa</i> .
* <i>C. coccinea</i> .
* <i>C. heterophylla</i> .
<i>C. lucumaeifolia</i> .
β <i>stupea</i> .
<i>C. lanceolata</i> . |
| Ramus C. <i>Lancifoliae</i> | { <i>C. lancifolia</i> .
α <i>vera</i> .
β <i>rubra</i> .
γ <i>obtusata</i> .
δ <i>Calisaya</i> .
ϵ <i>discolor</i> .
* <i>C. Forbesiana</i> .
<i>C. amygdalifolia</i> . |

II—STIRPS CINCH. RUGOSAE:—

- | | |
|----------------------------|--|
| Ramus A. <i>Eurugosae</i> | { <i>C. Pitayensis</i> .
α <i>colorata</i> .
β <i>Trianae</i> .
γ <i>pallida</i> .
δ <i>Almaguerensis</i> .
* <i>C. corymbosa</i> .
<i>C. rugosa</i> .
β <i>crispa</i> .
<i>C. Mutisii</i> .
<i>C. hirsuta</i> . |
| Ramus B. <i>Pahudianae</i> | { <i>C. Carabayensis</i> .
<i>C. Pahudiana</i> .
<i>C. asperifolia</i> .
<i>C. umbellulifera</i> .
<i>C. glandulifera</i> .
<i>C. Humboldtiana</i> .
β <i>conglomerata</i> . |

²² Weddell, Ann. Sci. Nat. Bot. 1870-71, 5th ser., XI, p. 346, XII, p. 24.

III—STIRPS CINCH. MICRANTHAE:—

- | | | |
|-------------------------------|---|---|
| Ramus A. <i>Scrobiculatae</i> | { | <i>C. australis.</i>
<i>C. scrobiculata.</i>
<i>C. Peruviana.</i>
<i>C. nitida.</i> |
| Ramus B. <i>Eumicranthae</i> | { | <i>C. micrantha.</i>
α <i>Huanucensis.</i>
β <i>Reicheliana.</i>
γ <i>affinis.</i>
δ <i>calisayoides.</i>
ϵ <i>rotundifolia.</i> |

IV—STIRPS CINCH. CALISAYAE:—

- C. Calisaya.*
 α *vera.*
 β *microcarpa.*
 γ *Boliviana.*
 δ *oblongifolia.*
 ϵ *pallida.*
C. Josephiana.
C. elliptica.

V—STIRPS CINCH. OVATAE:—

- | | | |
|-----------------------------|---|---|
| Ramus A. <i>Succirubrae</i> | { | <i>C. purpurea.</i>
<i>C. rufinervis.</i>
<i>C. succirubra.</i>
<i>C. erythroderma.</i>
* <i>C. rosulenta.</i>
* <i>C. erythantha.</i> |
| Ramus B. <i>Euovatae</i> | { | <i>C. ovata.</i>
α <i>genuina.</i>
β <i>vulgaris.</i>
γ <i>pallescens.</i>
<i>C. palatba.</i> |
| Ramus C. <i>Cordifoliae</i> | { | <i>C. cordifolia.</i>
* <i>C. lutea.</i>
* <i>C. platyphylla.</i>
* <i>C. subcordata.</i>
<i>C. rotundifolia.</i>
<i>C. Tucujensis.</i>
<i>C. pubescens.</i>
* <i>C. Pelletieriana.</i>
* <i>C. obovata.</i>
<i>C. purpurascens.</i>
* <i>C. decurrentifolia.</i>
<i>C. Chomeliana.</i>
<i>C. Barbacoensis.</i> |

* The names of subspecies are distinguished by an asterisk.

Of this large number of species and subspecies a very small number yielded commercially valuable barks, these barks being collected in five different regions in South America. They were as follows:—

- | | |
|--|----------------------------|
| I. <i>C. officinalis</i> var. α <i>Condaminea</i> | } yielding crown barks. |
| " β <i>Bonplandiana</i> | |
| " γ <i>crispa</i> | |
| II. <i>C. succirubra</i> (Pavon), yielding red bark. | |
| III. <i>C. Pitayensis</i> etc. | } yielding Colombian bark. |
| <i>C. lancifolia</i> | |
| <i>C. cordifolia</i> | |
| IV. <i>C. nitida</i> | } yielding gray bark. |
| <i>C. micrantha</i> | |
| <i>C. Peruviana</i> | |
| V. <i>C. Calisaya</i> , yielding yellow bark. | |

Weddell's classification underwent a number of modifications at the hands of later botanists. Kuntze divided the genus into four classes, which corresponded pretty closely with the stirpes of Weddell; he, however, regarded only *C. Calisaya* Weddell (*C. Weddelliana* Ktze.), *C. micrantha* Pavon (*C. Pavoniana* Ktze.), *C. succirubra* Pavon (*C. Howardiana* Ktze.), and *C. Carabayensis* Weddell (*C. Pahudiana* (How.) Ktze.) as true species, and all others, including *C. officinalis*, as hybrids. The *C. officinalis* of Hooker he thought a regular, the *C. Ledgeriana* Moens, an irregular, hybrid of *C. Calisaya* and *C. micrantha*. More recent quinologists are inclined to look upon *C. officinalis* Hook. and *C. Ledgeriana* Moens as genuine species, or at least subspecies, and some think *C. Josephiana* Weddell also a distinct species.

VII. THE CINCHONA BARKS OF COMMERCE

Originally, cinchona barks came exclusively from Loxa. Then, as other cinchona-bearing regions were discovered, barks were shipped from other places, distant from the original source and from one another. It was the custom of Spanish merchants to classify the drug according to the place where the tree yielding it grew or from its port of shipment. This system was satisfactory as long as the number of species was small and their geographical regions narrowly circumscribed; but later, as the number of bark-yielding species grew, the older names were in many cases retained. Because of certain similarities in the barks, confusion ensued, and

the trade-names no longer had any meaning. As an example: the name *Loxa bark* came to be given not only to those barks which came from that province but also to others which were derived from the province of Huanuco; and, again, other barks which came from the same neighborhood were given different names. The bark-dealers in South America were not more careful or better informed as to the geographic sources of the drug; they gave the name *Loxa bark* to all slender, gray barks, irrespective from where they came, while those somewhat older and larger were designated *Lima bark*.

Classification according to botanic origin, which would have been the most scientific and most rational, was out of the question, for the reason that the precise origin of many of the barks was not known or they were but obscurely traced to their native tree. Some pharmacists, indeed, thought that the valuable barks, that is, those that yielded quinine and cinchonine, came from the same species of *Cinchona*. Even so able a pharmacognosist as Guibourt was disposed, in the beginning, to incline to the view that they all came from varieties of *Cinchona lancifolia*, resting his opinion upon the statement of La Condamine that at Loxa he was informed upon good authority that the trees yielding the yellow and red barks respectively were not distinguishable by the eye. Authorities also differed at various times in the ascription of barks to various species. Finally, a means of classification was evolved which was based upon the color of the barks, and they were divided into three classes, the *pale*, the *yellow*, and the *red*. The South American traders laid stress upon the color of the bark as in a measure indicative of its quality, adding to this the taste and odor. The orange-colored barks were the most highly esteemed, and the variation in shade from this to the palest yellow or gray indicated a corresponding progressive diminution in value. Barks of a dark color between red and yellow were considered to have been derived from inferior species, to have been improperly prepared, or to have suffered from injurious exposure to air or moisture. The taste of a good bark was bitter and very slightly acid but not acrid, nauseous or highly astringent. The odor should not be very strong, but should be decided, and not disagreeable; it was a decided factor in judging some of the better barks. The

appearance of the epidermis was also determinative, and the differences it exhibited led to a commercial classification of the barks as follows:

1. Negrilla, blackish.
2. Crespilla, crisped.
3. Pardo-oscuro, dark leopard-gray.
4. Pardo-clara, bright leopard-gray.
5. Lagartijada, silver or lizard-colored.
6. Blanquissima, very white.
7. Cenicienta, ash-colored.

Before the discovery of the alkaloids, quinine and cinchonine, the smaller barks, derived from the branches or twigs, were preferred although La Condamine learned at Loxa that originally the "strongest," the trunk barks, were mostly in demand. It is probable that the greater difficulty encountered in drying and otherwise preparing the thicker barks led the collectors to select the twigs. It was also supposed, for some reason, that the small barks were medicinally more potent. Pomet, in 1694, recommended only the "*petites ecorces fines, noirâtres et chagrinées au dessus, parsemées de quelques mousses blanches,*" and the druggist Berlu stated that in 1724 the thick, flat trunk barks were much less valued in the London drug market than the barks of the twigs. After the discovery of the cinchona alkaloids and the introduction of assay methods, it was found, however, that the flat Calisaya and other trunk barks were usually richer in quinine, so that these came again into demand, although the smaller kinds were not altogether rejected.³³

Hand in hand with the chemical investigation of the cinchona barks went an intensive pharmacognostic study, in which, in the earlier period, the names of Laubert, Lambert, Goebel, Kirst, and, especially von Bergen are preëminent. Von Bergen was a drug broker in Hamburg, and his extended experience in the handling of cinchona barks had furnished him with a wealth of material regarding their various characteristics. This he published for the benefit of the scientific world in 1826 in his '*Versuch einer Monographie der Chinarinden,*' to which he added a supple-

³³ Goebel & Kunze, *l. c.*, p. 105.

ment consisting of seven colored plates of commercial barks. "The description of these barks," says Flückiger, "accomplished all that is possible without the aid of the microscope." Weddell's researches into the botanical and geographical distribution of the cinchona species have been recounted in another place. His 'Histoire Naturelle des Quinquinas' marks an epoch in pharmacognosy, also, for it was the first work to give illustrations of the anatomical structure of the various barks, and to show that the structure and chemical composition of the barks go hand in hand. In 1854 Delondre and Bouchardat contributed their 'Quinologie,' a quarto of forty-eight pages and twenty-three plates, the latter giving colored figures of more than thirty different true and false cinchona barks. Augustin Pierre Delondre was a quinine manufacturer who had visited South America, where he accidentally met with Weddell, in whose company he visited the forests of Santa Ana near Cuzco. Appollinaire Bouchardat was an apothecary and chemist. Hermann Karsten also made valuable contributions to the science of quinology. The first four parts of his 'Florae Columbiae terrarumque adjacantium specimina selecta,' published in 1858, gives colored figures of a number of cinchonas and allied species, and in 'Die medizinischen Chinارينden Neu Granadas' he gives, besides the text, two plates representing the microscopic structure of a number of cinchona barks. The name of John Eliot Howard must also be mentioned in this place; besides publishing his 'Illustrations of the Nueva Quinologia of Pavon' in 1862, he contributed many papers on the barks to the 'Pharmaceutical Journal of London.' Guibourt's 'Histoire des drogues' and Pereira's 'Materia Medica,' in their several editions, also furnish descriptions of the various barks found in commerce. It is upon the works mentioned, assisted by various pharmacopoeias and dispensaries, that the following descriptions are based. We deal here only with the barks derived from South America, before the advent in Europe of those obtained from the cultivated plants in Java and India.

The commercial classification of cinchona barks into *pale*, *yellow*, and *red*, was based upon the color of the powder, and it was the one that prevailed for many years. It was not a sharp one,

for the colors graduated into one another, and it was not always easy to tell whether a given bark belonged to one or the other of the classes. Other characteristics, however, exhibited by the entire bark, served as criteria in the majority of cases, so that for practical purposes the system was a fairly satisfactory one.

I. PALE BARK.

1. LOXA BARK.

Crown Bark.

Quinquina de Loxa.

Loxa China.

Kron-China.

This was the *original* or *true crown bark*, or *old Loxa bark*. Regarding the origin of the term *crown bark*, Pereira relates the following anecdote:³⁴—In October, 1804, the English captured a Spanish galley which was returning from Peru, among whose freight were found many parcels of cinchona bark, two sorts of which were distinguished by their appearance and mode of packing. Two of these chests bore the inscription “para la real familia”—for the royal family—and were lined with sheet iron. The drug contained in these was in fine quills, about thirteen inches long, and tied up into bundles about three inches in diameter. The other sort bore the mark “para la real corte”—for the royal court. The circumstance that these choice barks were destined for the King and his entourage led to their being designated *crown barks*.³⁵

In his ‘Monographie’ Bergen gives the following description of this bark:—Cylindrical, strongly rolled, six to fifteen inches long, two lines to an inch in diameter, half a line to two lines in thickness. Outer surface more or less rough, seldom strongly wrinkled longitudinally, but marked with numerous transverse fissures, these fissures usually running round the bark and dividing it into ring-like segments with somewhat raised edges; these fissures are not distinct in the outer quills. In the largest rolls the surface is very rough, sometimes warty. The epidermis is dark gray, sometimes almost black, at times ash-colored or inclining to fawn; it exhibits lichens of a whitish color, sometimes

³⁴ Pereira, J. *Elements of materia medica and therapeutics*. 3d edition, 1853, II, p. 1863; Goebel & Kunze., *l. c.*, pl. 5, figs. 1–9; pl. 6, figs. 1–8.

³⁵ Howard, *Pharm. Jour.* XI, p. 494.

so numerous as to hide the proper color of the bark, giving the outer surface a light gray appearance. Inner surface smooth and uniform in texture, of a cinnamon color, occasionally showing a reddish tinge. The smaller quills yield a smooth, the larger a somewhat fibrous, fracture. The bark has a firm consistence, and when cut exhibits a resinous appearance. It has a characteristic odor, which Guibourt compares to that of damp woods and von Bergen to that of tan bark. Taste bitterish, astringent, acidulous. Powder of a dull cinnamon color.

In the edition of the 'Histoire des Drogues' of 1850 Guibourt describes four chief varieties of Loxa bark, which he names: 1. *Quinquina de Loxa gris compacte*; 2. *Quinquina de Loxa brun compacte*; 3. *Quinquina de Loxa rouge fibreux du roi d'Espagne*; 4. *Quinquina de Loxa cendre*.

Von Bergen's description applies to the first two. The third differs from the ordinary Loxa bark in its fibrous texture and slight astringency. It was rare in commerce, the fourth variety being the one almost exclusively occurring in the French drug market. This fourth variety Guibourt describes as occurring in very thin quills, usually much rolled, only slightly rough on the external surface with minute transverse fissures, generally covered with a whitish coat which gives it a light gray color, internally very smooth, reddish; fracture finely fibrous. Taste bitter and astringent, odor marked. The larger pieces, derived from the trunk, may have a thickness of two lines, and resemble somewhat Calisaya bark; the outer surface is scarcely rough and often longitudinally wrinkled; it is readily distinguished by the fineness of its texture and the smoothness of its inner surface. Guibourt believed it to be derived from *C. macrocalyx*.

In the English trade ⁸⁶ Loxa bark was distinguished as:

1. *Picked Crown Bark*, consisting of the finest, longest and thinnest quills.

2. *Silvery Crown Bark*, somewhat larger than the preceding and possessing a whitish, silvery epidermis due to the presence of lichens.⁸⁷

3. *Leopard Crown Bark*, exhibiting a speckled appearance,

⁸⁶ Pereira, l. c., p. 1638.

⁸⁷ Laubert, Memoir in Lambert's Illustrations of the genus Cinchona, p. 78.

whence its name, from the presence of whitish lichens scattered over the dark brown epidermis.

In the last edition of Pereira's 'Materia Medica,' which appeared after the author's death in 1857, ed. 4., the following varieties of *Loxa* bark are described:—

1. *Original or Old Loxa Bark*.⁸⁸—This was the original *crown bark*, seized by the English in 1804. Pereira describes it as coming into the market in slender quills, 13 inches long, tied up in bundles about 3 inches in diameter; it came in this original form for many years, and was later found so occasionally in seroons of commercial crown bark. It was believed that the bark was originally derived from *C. Condaminea* var. *vera* Weddell. This tree became exhausted, and the variety of crown bark which came afterward was probably derived from other varieties of *C. Condaminea* or from other species of *Cinchona*.

2. *White Crown Bark*.—In small and large quills. The small quills were silvery on the surface from the presence of lichens and had numerous transverse cracks. The larger had no transverse fissures, but exhibited longitudinal rents which gave it a ragged appearance, the exposed interior showing a lustrous, satin-like surface. It was assigned to *C. Condaminea* var. *lucumaeifolia* Weddell, the *C. lucumaeifolia* of Pavon.

3. *H. O. Crown Bark*.—The name of this bark was derived from the brand "H. O." with a crown, which was adopted at the time of the Spanish dominion in South America for two different kinds of bark which were later included under the general title "crown bark." According to Pereira,⁸⁹ it was the crown bark usually found in commerce in his time. It was imported from Payta. It occurred in quills 6 to 15 inches long, 2 lines to an inch in diameter, $\frac{1}{3}$ line to 2 lines thick. The quills varied somewhat in appearance: Some were without lichens, were very thin, shrivelled and brown externally, with many longitudinal wrinkles but few transverse fissures, the internal surface of cinnamon color, fracture pale yellow; other quills were larger, coarser, more or less grayish externally from lichens, and exhibited many transverse fissures, some of which extended around the quills; still others

⁸⁸ Pereira, l. c., p. 1638; Weddell, l. c., p. 41, 74.

⁸⁹ Pereira, l. c. p. 1639.

were twisted, were patchy black and white exteriorly from adhering lichens. Howard believed that the bark was derived from *C. glandulifera*, but its botanic origin was not certainly known.⁹⁰

4. *Ashy Crown Bark*.—*China Pseudo-Loxa* or *Dunkle Ten-China* of von Bergen; *Dunkle Jaen China* of Goebel; *Quinquina de Loxa cendré* of Guibourt. This was imported from Lima in seroons and bags. Pereira⁹¹ warns against confounding this with the *ash* or *pale Jaen bark*, which is quite a different variety. Guibourt included both the *ash* or *pale Jaen bark* and *ashy crown bark* under the name *quinquina de Loxa cendré*, the former constituting his *variety A*, the latter his *variety B*. The bark came in quills about the size of the finger, the external surface being mounted with white, gray, and black patches of lichens, many of the quills displaying rusty warts or fungoid tubercles, perhaps produced, Pereira suggests, by the puncture of an insect. The epidermis was marked by longitudinal wrinkles and transverse fissures; internal surface orange or cinnamon in color. Taste bitter. Mr. Howard found the bark to be identical with a specimen in Pavon's collection marked "Cascarilla con hojas redondas de Quiebro de Loxa," ascribed to *C. rotundifolia* of that botanist, the *C. cordifolia* var. *rotundifolia* of Weddell. According to von Bergen the bark agreed with one in Ruiz's collection said to have been obtained from *C. lancifolia* of Mutis. Pereira says, however, that it differed from the *lancifolia* barks with which he was acquainted.

5. *Wiry Loxa Bark*, *Twiggy Loxa Bark*.—This bark, which was imported from Payta in seroons, occurred in the form of very slender, wire-like quills, smoothish and brown internally, fairly smooth, with scarcely any transverse cracks and without adhering lichens exteriorly.⁹² Many of the quills were lined by a thin shaving of pale yellow wood. Fracture short and resinous, taste but slightly bitter and very astringent. It was a very inferior bark. Pereira surmises from the remarkable slenderness of the quills that the wiry bark might be the *cascarilla delgada* or *delgadilla* (slender bark), or the *cascarilla fina delgada* (fine slender

⁹⁰ Howard, Pharm. Jour. XII, p. 128.

⁹¹ Pereira, l. c., p. 1639.

⁹² *Ibid.*, p. 1640.

bark) which, according to Ruiz and Pavon, was obtained from *C. hirsuta*. The small, transverse cracks which were said to render the surface of the *delgada* rough were absent. Pereira found that in its smoothness wiry Loxa bark resembled somewhat the kind called in South America *negrilla*.

Early analyses showed that the Loxa barks varied much in their yield of alkaloids; they contained both cinchonine and quinine, the former predominating. Later analyses revealed the presence of both cinchonidine and quinidine, sometimes in considerable proportion. The larger barks yielded, in all the varieties, more alkaloids than the smaller.

2. LIMA BARK.

Huanuco Bark.⁴³

Gray Bark.

Silver Bark.

Quinquina de Lima.

China Huanuco, Grave China.

Cinchona cinerea.

The discovery of the cinchona trees in the central regions of Peru brought this bark into notice about 1779. According to Pöppig, trade in the barks of Huanuco began in 1785 but had almost come to an end in 1815. According to Pereira, it first became known in Spain in 1799,⁴⁴ when 180 chests of it were brought by the frigate *La Veloz* to Santander. Ruiz was appointed to examine the cargo. He found, mingled with the barks of *C. nitida* and *C. lanceolata* and those of the species which Tafalla designated as "similar to Calisaya," a thick bark up to that time unknown to the botanists of Peru.

The name *Lima bark* was given because the bark passed into commerce through the city of Lima. Huanuco was the town in the neighborhood of which it was collected. Cuchero also furnished the bark. It came to Europe in seroons and chests. It always occurred in the form of quills, which were usually coated. Two sorts were found in English commerce, usually coming mixed but sometimes separately; they were known respectively as *fine gray bark* and *inferior* or *coarse gray bark*. According to Howard, the *fine* bark was derived from *C. nitida* and the *coarse* from *C. micrantha*.

⁴³ Pharm. Jour. XI. p. 129; Goebel & Kunze, l. c. pl. 10, figs. 1-5.

⁴⁴ Pereira, l. c., p. 1633.

1. *Fine Gray Bark*.—This was the *Quinquina rouge de Lima* of Guibourt, the *China Huanuco* of Goebel,⁹⁵ the *Cascarilla Peruviana* or *Quina cana legitima* of Laubert. Pereira ⁹⁶ gives the following as the characteristic properties of this bark:—quills from 3 to 15 inches long, diameter from 2 lines to $1\frac{1}{4}$ or even 2 inches, thickness $\frac{1}{3}$ line to 5 lines. At the edge of most of the perfect quills occurred a sharp, oblique cut; cuts of this kind were rarely found on other barks; quills frequently somewhat spirally rolled. The epidermis presented numerous short, irregular, transverse cracks, not forming rings, however, as in the *Loxa* bark, and with flat edges, scarcely separated or everted. Longitudinal wrinkles or furrows, which in the thicker pieces often penetrated completely through the outer coating of the bark, also occurred on the epidermis. Outer surface clear or silver-gray or whitish, a uniform whitish-gray in the smaller quills, the large quills with a covering due to adhering lichens. Inner surface of the small quills smooth, of the larger, fibrous; color reddish- or rusty-brown. The inner layers of the bark often soft and friable. Fracture smooth and resinous in appearance. The odor is clay-like or sweetish, a peculiarity of this variety of bark, according to von Bergen. Taste bitter, aromatic, astringent, not disagreeable. Powder deep cinnamon-brown. Howard's analysis showed this bark to contain 2.113 per cent of alkaloids, of which quinine constituted 0.571 per cent, cinchonine 1.4 per cent and quinidine 0.142 per cent.

2. *Coarse or Inferior Gray Bark*.—This was the *Quinquina de Loxa gris brun* of Guibourt, and the *Cascarilla provinciana* of Pöppig. The bark of *C. micrantha*; Guibourt describes it thus:—In the form of long tubes, well rolled, varying in size from that of a writing-quill to the little finger. It very often shows longitudinal wrinkles due to drying. The external surface somewhat rugose, often nearly destitute of transverse fissures, in general of a deep gray tint but with white or black spots, bearing here and there the same lichens as the *Loxa* barks. The liber deep brownish-yellow and as if formed of agglutinated fibres. Taste bitter, astringent, acidulous, and aromatic. According to Howard, this

⁹⁵ Goebel & Kunze, *l. c.*, pl. 7, figs. 1-4.

⁹⁶ Pereira, *l. c.*, p. 1633.

bark is peculiar for its general woody texture, a characteristic very marked upon reducing it to powder; the only hard portion of the *fine* gray bark is a resinous layer lying between the inner and outer coats. He says also that it is thinner than the *nitida* bark, wrinkled longitudinally, and glaucous externally. It yields a pale decoction from which a small flocculent deposit separates on cooling, while the decoction of the *fine* bark is brown and gives a copious deposit. The 'Edinburgh Pharmacopoeia' referred all Lima bark to *C. micrantha*; but the observations of Guibourt, Pereira, and Howard left little room for doubt that it is only the *coarse* bark which is derived from that species, the *fine* bark coming from *C. nitida*. Howard's analysis of the *coarse* bark yielded 1.773 per cent of alkaloids, of which 0.243 per cent was quinine, 0.28 per cent quinidine, and 1.25 per cent cinchonine.

3. JAEN BARK.

Ash cinchona.

China Jaen or Blasse Ten-China of von Bergen.

Quinquina de Loxa cendré of Guibourt.⁹⁷

Cascarillo palido of Ruiz.

This bark derived its name from the province of Jaen de Bracamoros, not far from Loxa, where large quantities were collected. It is not known at what date it was introduced into commerce, but von Bergen states that he found specimens of it in an old collection of drugs made in 1770. It was usually imported in chests, but also in seroons. Pereira is convinced that its source was *C. ovata* var. *α vulgaris* of Weddell.⁹⁸ It was met with in quilled form only, the quills being somewhat thick, 4 to 16 inches long, 3½ lines to one inch in diameter, ½ to 2 lines thick. The quills were very crooked, more or less arched and twisted. The epidermal surface exhibited a few transverse and some faint longitudinal cracks. The outer surface varied between ash-gray, whitish-gray, and pale yellow, diversified with blackish or brownish spots. When the outer coat was rubbed off the color inclined to yellow, a yellowish or straw color being characteristic of the bark when viewed in mass. The exterior layers had a soft and spongy texture and were easily scraped off by the finger-nail.

⁹⁷ Guibourt, *Histoire des drogues*, 4th ed., III, p. 152.

⁹⁸ Pereira, *l. c.* p. 1636; Howard, *Pharm. Jour.*, XII, p. 126; Guibourt, *l. c.*, p. 161; Goebel & Kunze, *l. c.* pl. 10, figs. 6-9, pl. 12, figs. 1-5; Weddell, *l. c.* p. 74.

The inner surface was either smooth or uneven and splintery and usually of a dull cinnamon color. The bark was very brittle, the fracture being smooth in the smaller quills, more or less uneven and sometimes splintery in the larger; it exhibited no resinous appearance. Odor sweetish and comparable to that of tan. Taste acidulous, bitter, slightly astringent, not disagreeable.

Von Bergen describes a *dark Jaen bark* (dunkle Ten-China) or *pseudo-Loxa bark*. It resembled the *Loxa* variety in some particulars but was distinguishable from it by the oblique or bent shape of the quills and the uneven, fibrous or splintery inner surface. It came almost always in small pieces. Pereira believed it to be identical with the *ashy crown bark*. The analyses of this bark yielded varying results. Howard obtained, from a rather poor-looking specimen, 0.61 per cent quinidine and 0.86 per cent cinchonine. From some flat pieces he obtained 0.86 per cent cinchonine and 1.2 per cent quinidine. Pereira states that Goebel and Kirst obtained 12 grains of quinine from one pound of the bark and Winckler 28 grains from 16 ounces.

4. HUAMALIES BARK.

The name of this bark is derived from the province of Huamalties, lying in the interior of Peru to the north of Huanuco and within the region explored by Ruiz and Pavon.⁹⁹ Guibourt names it *Quinquina de Huamalties*; von Bergen, *China Huamalties*, *Braune China*, Goebel, *China Huamalties*, *Guamalties* or *Abomalties*, and Geiger, *Braune China*, *China Huamalties*, *China fusca*. In French commerce it was known as *quinquina Havane*.

Von Bergen expresses the opinion that the Huamalties bark was introduced into Europe at the same time as was the *silver bark*, toward the end of the eighteenth or the beginning of the nineteenth century. It was frequently carried direct from Lima to Hamburg in 1803. It appears to have enjoyed a high reputation in Germany. Pereira¹⁰⁰ states that it was not used as a distinct kind in England and that most druggists were unacquainted with it, but that some of the English merchants bought considerable quantities for the foreign market, particularly Germany.

⁹⁹ Howard, *l. c.*, p. 61, 126; Goebel & Kunze, *l. c.*, pl. 10, figs. 1-5; Weddell, *l. c.*, p. 74.

¹⁰⁰ Pereira, *l. c.* p. 1635.

According to Pereira, Huamalies bark presented so many different appearances at different ages as to defy classification.¹⁰¹ Some of the fine quills, he says, might readily be mistaken by inexperienced persons for Loxa bark, while he knew an experienced dealer to mistake it for what he called "fimsy" red bark. The 'United States Dispensatory' of 1858 gives the following general description of the bark, derived from a German source:—"It is in quills and flat pieces. The quills are from 3 lines to $1\frac{1}{2}$ inches in diameter, from 5 to 10 inches long, and from $\frac{1}{2}$ a line to 3 lines thick. The flat pieces, which are usually only fragments of the largest quills, are from 1 to 2 inches broad and 6 to 12 inches long. In general all the layers of the bark are present, but sometimes the outer coat and even the whole part of that usually called the epidermis in our description of bark (including those outer layers which are destitute of vitality, having been thrown outward by the annually renewed layers beneath them), are wanting in spots, though very seldom entirely absent. The epidermis is comparatively thin, very brittle, soft and spongy. The outer surface in the small and middling quills is sometimes nearly smooth but usually marked with wavy, longitudinal wrinkles and beset here and there with warts. These warts are abundant upon the thick pieces, which they sometimes almost entirely cover. Transverse fissures are seldom found, and only in the thick pieces. The color of the epidermis is usually grayish-fawn, here and there passing into a rusty brown; but in the thicker pieces, in which the warts are abundant, it is between a liver and chestnut color, often mixed with a tinge of purple. When the epidermis is wanting, the color is often a full ochre yellow. The inner surface is sometimes uniform and almost smooth, sometimes slightly fibrous, rarely splintery. The color of this surface is rusty brown, occasionally reddish, and in the fibrous or splintery pieces of an ochre yellow. The fracture in the smaller pieces is rather even, in the larger presents short fibres and is sometimes even splintery. The odor of the bark is feeble but agreeable, the taste somewhat aromatic, bitterish and slightly astringent. The powder is of a full cinnamon color."

Pereira,¹⁰² as a means of orientation, distinguished several

¹⁰¹ Pereira, l. c. p. 1635.

¹⁰² *Ibid.*

varieties of the bark according to the different appearance presented by the pieces. Some of the finer quills (*Huamalies simulating Loxa bark*) resembled those of *Loxa bark*, but were dull gray externally, had fewer transverse cracks, were smoother or finely striated or wrinkled longitudinally and, when broken, appeared nearly white in the interior; this is the *dull gray Huamalies bark*, the *quinquina Huamalies gris terne* of Guibourt. Another kind which frequently occurred in the *Loxa bark* of commerce he had heard called *rusty crown bark*. It was in larger quills with a whitish or grayish epidermis, striated or furrowed longitudinally but devoid of transverse cracks and easily scratched off with the nail; this was the *thin or reddish Huamalies bark*, the *quinquina Huamalies mince et rougeâtre* of Guibourt; on some of the pieces occur rusty warts which, when numerous, were arranged in irregular, longitudinal lines. A third variety was flat or arched, with a whitish epidermis, and large red warts from which the epidermis had been removed; this was known as *verrucous white Huamalies bark*. Finally, the *verrucous rusty Huamalies* was that represented by quills or flat pieces, with the outer surface an ochre-red or rusty color, warts arranged for the most part longitudinally and almost totally devoid of transverse cracks.

Huamalies bark was at one time regarded as derived from *C. pubescens* Vahl, the *C. purpurea* of the 'Flora Peruviana,' but Pereira and Howard¹⁰³ were led by careful observation to refer it to the *C. Condaminea* var. *Chahuarguera* of De Candolle which Weddell considered as identical with his *C. Condaminea* var. *vera*.

II. YELLOW BARK.

Cinchona flava.

Cinchona regia.

Royal or Genuine Yellow Bark.

Quinquina Calisaya ou jaune royal, Guibourt.

China Regia, Königs-China, von Bergen.

China Calisaya, Goebel.¹⁰⁴

Among a considerable number of cinchona barks of a yellow color or yielding a yellow powder, one was pre-eminent for its yield of quinine, on account of which it was termed *genuine yellow bark*, to distinguish it from the inferior varieties. It was also

¹⁰³ Pereira, l. c. p. 1635; Howard, l. c. p. 61.

¹⁰⁴ Goebel & Kunze, l. c. pl. 7, figs. 5-6, pl. 8, figs. 1-6.

known as *royal yellow bark*, *cinchona regia*. It was introduced into Europe probably toward the end of the eighteenth century. Pereira¹⁰⁵ mentions Dr. Relph as stating that in a letter from a Spanish merchant established at Cadiz, dated September, 1789, it is observed that the *yellow bark* had lately become known there—"The first parcel which arrived here was tried at Madrid, and was immediately bought by the King's order for his own use." Further, according to Pereira, Murray first saw it in Frankfort a. M. in 1790, and afterward received it under the name of *Cortex chinæ flavus*, and to prevent confusion proposed to term it *royal yellow bark*, *cortex chinæ regius flavus*. The name *Calisaya* was given it in South America; at what period that term began to be used in Europe is not known.

It was known that *Calisaya* bark was produced in greatest abundance in the Bolivian province of La Paz,¹⁰⁶ that it was originally shipped from Buenos Ayres as well as from ports on the Pacific, but that at a later time it came chiefly, if not exclusively, from the port of Arica, whither it was brought from the interior provinces of Bolivia. In La Condamine's account of the *cinchona*, several times referred to, occurs the statement that anterior to the exploitation of the febrifuge at Loxa, the Jesuits of La Paz had sent to Rome an intensely bitter bark known as *quinquina*. La Condamine supposed this to have been the bark of the Peruvian balsam tree (*Myroxylon Pereiræ* Klotzsch, *Tolui-fera Pereiræ* Royle), which the natives called *quinquina*. Some pharmacognosists were disposed to believe that this Bolivian bark of La Condamine's was really a *cinchona* of the *Calisaya* type, that, for some reason or other it fell into disuse, then again entered commerce, and its re-introduction in the eighteenth century regarded as an original discovery:—there is no way of deciding this question one way or the other. It is interesting to note, in connection with this subject, however, that Pomet, in his history of drugs published in 1694, speaks of a bark more bitter than that of Loxa, which was obtained from the province of Potosi, bordering upon that of La Paz.

In the absence of positive information, authors differed for

¹⁰⁵ Pereira, l. c. p. 1621.

¹⁰⁶ Pharm. Jour. XI, p. 215.

many years as to the particular species which yielded Calisaya bark. Mutis had given the name *yellow bark*, from its color alone, to *C. cordifolia*, and this, by some, was regarded as evidence sufficient to justify the acceptance of that species as the source of this particular drug. Unfortunately, it was demonstrated that no Calisaya bark was brought from those regions where the *C. cordifolia* is most abundant. Many writers ascribed the Calisaya to *C. lancifolia*, on the authority of Mutis himself, who asserted that it was unquestionably obtained from that species. Ruiz frankly acknowledged that he was unacquainted with the source, but thought that it might be derived from *C. lanceolata*, which is now acknowledged to be identical with *C. lancifolia*. It was one of Weddell's objects in his exploration of the Bolivian cinchona forests to settle this mooted point. He found that the *true yellow bark* was derived from a tree which he discovered in 1847 and to which he gave the name *Cinchona Calisaya*. He found the tree inhabiting the warm forests on the declivities bordering the valleys of Bolivia and southwestern Peru, the chief localities being the Bolivian provinces of Enquisivi, Yungas de la Paz, Larecaja or Sorata, Caupolican or Apolobamba, and the Peruvian province of Carabaya.¹⁰⁷ It grows at altitudes of from 5000 to 6000 feet above sea level, and, when full grown, has a trunk often twice the thickness of a man's body, and a splendid crown of foliage appearing above all the other trees of the forest. There is a shrub-like variety of the tree which Weddell named β *Josephi-ana*, in memory of Joseph de Jussieu, who first noticed it; it is known in its native country as *Ichu-Cascarilla* or *Cascarilla del Pajonal*, the latter name being given it from the circumstance that it grows on the borders of mountain meadows, in the same regions as the larger tree. It reaches a height of from six to ten feet. Weddell also distinguished as varieties of *C. Calisaya* the forms known in Bolivia as *Calisaya zamba*, *morada*, *verde*, or *alta* and *blanca*.¹⁰⁸ Mention should be made here of an important species of *Cinchona* which, when it came to the notice of quinologists, was found to be more productive of quinine than even *C. Calisaya*. This is *Cinchona Ledgeriana*. Charles Ledger was an

¹⁰⁷ Weddell, *l. c.*, p. 31.

¹⁰⁸ *Ibid.*, p. 108.

English merchant who, since 1845, had resided at Puno, the chief city of the Peruvian province of Carabaya, where he engaged, among other things, in the exportation of cinchona barks. In his endeavors to secure the best bark he was told by the natives to secure one which they called *rojo*, or *red*, which in reality was a reddish-yellow. In 1851 he found the trees indicated on the banks of the Mamoré. In 1865 his agent, Manuel Incra Mamani, collected seeds of the plant near Pelucho, in the Bolivian province of Caupolicán, about 68° west longitude and 15° south latitude. The seeds were sent for sale to London, but found no purchaser among the English, when the Dutch government bought them for Java, where they successfully germinated. It was in 1874 that the large content of quinine was determined. Howard classified this plant as a variety of *C. Calisaya*, but Moens and Trimen regarded it as a distinct species, naming it *Cinchona Ledgeriana*.

The term *yellow bark* came to indicate only the valuable variety of barks of this color, the commercial name being *Calisaya*. Yellow barks from sources other than *C. Calisaya* were designated *false* or *spurious Calisaya*.¹⁰⁹ The officinal bark was divided into the *quilled* and the *flat*; these came sometimes mixed in the same seroon, sometimes separate.

The *quilled* variety was called by the Spaniards *Calisaya arrollada*. It occurred in *quilled* pieces from three inches to two feet long, from $\frac{1}{4}$ inch to 3 inches in diameter, and of a thickness varying with these dimensions. Epidermis brownish in color, partly or wholly concealed, silvery-white, whitish or yellowish lichens, longitudinally wrinkled and transversely fissured, often partially separated and in all cases easily separable from the inner or true bark. The epidermis in the larger pieces is thick, rough, showing deep indentations due to the transverse fissures, which often pass around the quills, and is composed of several layers separated from one another by a reddish-brown membrane. The epidermis gives a dark red powder, which is tasteless and inert. The bark itself is from one to two lines thick, compact, short-fibrous in texture, and when broken exhibits shining points, the terminations of short bast fibres which, under the microscope, present a characteristic form. These fibres separate readily when

¹⁰⁹ Weddell, l. c. p. 63.

the bark is powdered and produce an irritation when they penetrate the skin. The bark is brownish-yellow in color, tinged with orange. The taste less astringent than that of the pale bark but more intensely bitter. The external and internal regions of the bark differ somewhat in this quality of bitterness, the external being the more intense. Odor faint. The small quills bear some resemblance to those of some of the pale barks, but are distinguishable from them by their greater bitterness.

Flat Calisaya, the *Calisaya plancha* of the Spaniards.—This was derived from the trunk and large branches. In pieces varying in length, quite flat or but slightly curved, generally destitute of the epidermis. Outer surface irregular, exhibiting confluent longitudinal wrinkles and furrows and transverse ridges, somewhat darker in color than the inner surface, being of a brownish-fawn frequently with darker stains. The inner surface like that of the quilled variety. Fracture uniform throughout, differing from that of the quilled in possessing a more fibrous texture, and being less compact. The flat bark less bitter than the quilled. *Calisaya* bark deprived of the epidermis yielded from 3 to 3.5 per cent quinine, the percentage of cinchonine being much less.

Weddell mentions a variety of *Calisaya* bark with a dark-colored external surface, often entirely vinous black; this, he says, is the kind called in Bolivia *Calisaya zamba*, *negra* or *macha*. Another kind he found to possess a less uneven surface, sometimes semi-cellular in structure and paler in color; the Bolivians called it *Calisaya blanca*.¹¹⁰

False or Spurious Calisaya Barks.—These were barks which bore a resemblance more or less close to the true *C. Calisaya*, but were derived either from varieties of the species or from other species of the *Cinchona*.¹¹¹ Some of them were of little medicinal value, others were but little inferior to the true bark. They were gathered either as substitutes for the high-priced bark, or were used for purposes of sophistication. An inexperienced eye was in many cases readily deceived by these barks; but Weddell gave five characteristics by which a careful observer could distinguish the true *Calisaya* from all others.¹¹² These were:—

¹¹⁰ Weddell, *l. c.*, p. 35.

¹¹¹ *Ibid.*, p. 63.

¹¹² *Ibid.*, p. 30, 36.

1. The shortness of the fibres throughout the entire surface of the transverse fracture.
2. The ease with which these fibres may be separated.
3. The uniform fawn-color, without any white markings, in the thickness.
4. The great density of the bark:—when the finger-nail is drawn across it a shining track is left.
5. The depth of the depressions on the outer surface and the prominence of the ridges separating them.

These characteristics apply to the flat variety. For the quilled kind the intensely bitter taste is the surest guide. The spurious *Calisayas* are characterized by a deficiency in compactness, which led the French pharmacognosists and merchants to call them *Calisaya leger*. The spurious *Calisayas* met with in the literature are the following:—

1. The bark of *C. Calisaya* var. *Josephiana* of Weddell:—Not known as a distinct variety in the trade, but probably mixed in greater or less proportion with the true bark. Quills brown, grayish-black or slate-colored on the outer surface, covered with pale lichens. Inner surface irregular, in consequence of the difficulty encountered in separating it from the wood. Another kind of bark was obtained from the roots of the same variety, probably the remains of former trees. This was in short, flattish, undular, more or less contorted pieces, without epidermis, fibrous or almost smooth internally, slightly cellular externally, uniformly ochre-yellow in color, decidedly bitter but not intensely so as true *Calisaya*. Weddell says that the Peruvians called it *Ichu-Cascarilla*. These barks were medicinally not inferior to the genuine.

2. The bark of *Cinchona Boliviana*:—According to Weddell this was always mixed with true *Calisaya*, from which it was difficult to distinguish.¹¹³ However, it was not inferior to the true bark. Weddell describes the quills as being in all respects similar to those of the true *Calisaya*. Flat pieces consisted of inner bark only, of equal density with the true bark but not so thick, the furrows on the outer surface not so deep, and the ridges separating them more rounded. Color of the surface

¹¹³ Weddell, l. c. p. 50.

brownish-yellow fawn, greenish shades here and there. Inner surface reddish or orange-fawn. Fracture like that of Calisaya, but exhibiting spots of a light, almost white, color. Taste bitter, strong, and somewhat agreeable; this taste develops more rapidly on chewing than does that of the true Calisaya.

3. The bark of *C. ovata* var. *rufinervis* of Weddell:—The tree was called in Peru *Cascarilla Carabaya*; it inhabits Bolivia and the Peruvian province of Carabaya, where Weddell said the bark was extensively employed to adulterate the Calisaya.¹¹⁴ Distinguishable with great difficulty from the true bark, the outer coating of the quills differing in being somewhat thinner. In other cases it was finely wrinkled horizontally, had but few annular fissures, varied in color from light gray to deep brown, and was often completely covered with mosses and lichens. The outer coat generally easily separable from the inner, the uncovered surface being light brownish-fawn in color, smooth or marked with longitudinal depressions corresponding to rents or cracks in the outer coat. Inner surface grayish- or reddish-yellow, finely fibrous; resinous circle scarcely observable; taste quickly bitter, astringent. The *flat* kind variable in form, generally much lighter than the Calisaya. It sometimes consisted of the inner bark only, but frequently had fragments of the outer coat attached. Outer surface sometimes smooth, with a few transverse, linear depressions, fibrous at the bottom. Color grayish-fawn or reddish, sometimes marbled with darker shades. Inner surface dull grayish-yellow or brilliant orange, exhibiting fine parallel fibres. Transverse fracture more or less corky exteriorly, stringy-fibrous within or stringy-fibrous throughout. Taste considerably bitter, the bitterness rapidly developed with the fresher barks.

That *Carabaya Bark* was perhaps derived from *C. ovata* var. *β rufinervis*, which in Peru is called *Cascarilla Carabaya*, or from the variety *α vulgaris*, as Weddell suggested, or from any variety of *C. ovata* at all, is uncertain. Pereira¹¹⁵ says that it was first imported into London in 1846, and that it came from Carabaya through Islay or Arica. Pereira describes it as follows:—Thin and flimsy, of a more or less rusty color, and in some of the larger

¹¹⁴ Weddell, *l. c.*, p. 60, 85.

¹¹⁵ Pereira, *l. c.* p. 1629.

pieces very similar to the Huamalies bark. Quills about the thickness of the finger, variable in length, sometimes up to two feet, coated or uncoated, the uncoated sometimes with a dark or more or less tea-green tint. The *flat* pieces consisted of the liber alone, or of the liber with a portion of the cellular coat. Outer surface of the liber in some of the uncoated pieces blackish with rusty, round, flattish warts; this surface sometimes looked as if dusted over with a yellowish powder like gamboge or turmeric. Liber itself more or less orange in color, but the color in some pieces like that of *red bark*. The 'United States Dispensatory' of 1858 describes a variety of bark called *Carabaya* imported into the United States, as follows:—"In irregular pieces, some very small, the largest about 9 inches in length, generally very thin; for the most part destitute of epidermis, but sometimes with portions of the outer coat attached; on the outer surface, when uncoated, of a dull cinnamon hue, with spots of a different color sometimes much darker, more or less irregular from slight elevations and shallow depressions, somewhat furrowed longitudinally, seldom so transversely; on the inner surface of a lighter hue than on the outer, smooth and somewhat shining when viewed obliquely, with fine, compact, straight fibres; with a decided fibrous fracture, sometimes smooth towards the outer edge; and when handled readily yielding spicules which penetrate the fingers like those of *Calisaya*. In one specimen shown us by Messrs. Powers and Weightman the outer surface was almost completely covered with the sub-epidermic layer, with little or none of the epidermis itself, and was remarkably uniform in its aspect, though sometimes presenting numerous slight longitudinal wrinkles from drying and a few shallow, transverse impressions."

4. The bark of *C. scrobiculata*:—The younger bark of this tree was probably at one time imported mingled with the *pale* or *gray* barks, and the larger, *flat* pieces were fraudulently substituted for *Calisaya*.¹¹⁶ Pereira mentions two kinds, derived from two varieties of *C. scrobiculata*. These are:—

(a) The *Cuzco Bark*, or *Red Bark* of Cuzco, according to Delondre and Bouchardat. It also bore the name *Bark of St. Ann*. It was considered as having been derived from *C. scrobiculata* var.

¹¹⁶ Weddell, *l. c.*, p. 44.

Delondriana. Guibourt called it especially *Calisaya leger*, light *Calisaya*. It was collected in the province of Cuzco, in southern Peru, the center of its commerce being, according to Weddell, the town of Cuzco. Weddell¹¹⁷ gives the following description of it:—It consists generally of the liber and a thin layer of the cellular-resinous tissue; of less density than the *Calisaya*. Varies from 5 to 10 mm. (2 to 4 lines) in thickness. Outer surface smooth, with some transverse linear impressions, or more or less irregular, often with shallow cavities filled with fungal remains; in other cases raised into irregular warts or more rarely without the cellular coat, as in *Calisaya*, with confluent furrows digital in form, fibrous at the bottom, obscurely red in color. Inner surface of a uniform fine and straight grain and of a beautiful reddish-orange color. The transverse fracture more or less cork-like on the outside, depending upon the thickness of the cellular portion, very fibrous on the inside, with long, stringy, flexible fibres, lighter in color than the outer part. Longitudinal fracture displaying numerous splinters with shining points, less distinct than in the *Calisaya*, medullary rays more numerous and distinct. Taste strongly bitter, rapidly developed in the barks of middling size; perceptibly astringent.

(b) The bark of *C. scrobiculata* var. *genuina*, called *Peruvian Calisaya*, was imported from Lima. Pereira¹¹⁸ states that it occurred in the market in flat pieces, in color much like the true *Calisaya*, but the pieces thicker, and the bark smoother and the ridges dividing the furrows more rounded. Fracture fibrous. The larger pieces with a taste less bitter than that of *Calisaya*. In the eighth and ninth editions of the 'Unites States Dispensatory' was described a bark which had been imported into this country about 1848, and which had been assigned to a manufacturing chemist of Philadelphia by a commercial house in Valparaiso, with the information that it had been sent by Dr. J. Villamil and had been gathered in the forests of Huanuco; in the eleventh edition the opinion is expressed that this bark was the one under consideration. It is described as follows:—The pieces generally without the epidermis, which appeared to have separated sponta-

¹¹⁷ Weddell, *l. c.*, p. 56, 75.

¹¹⁸ Pereira, *l. c.*, p. 1628.

neously and, when retained, displayed the transverse fissures and longitudinal furrows characteristic of the Calisaya. Color and consistence of the bark the same as in the genuine; the bark even presented the shining spicules which characterize the latter, though they were less numerous and did not penetrate the fingers so readily. Taste very bitter.

5. The bark of *C. pubescens* var. *Pelletieriana*, of Weddell:—This was also known as Cuzco bark and as Arica bark,¹¹⁹ the latter name, derived from that of the port from which it was shipped, being the one by which it was first known in France and England. Pereira¹²⁰ says that it was originally introduced into Europe as *yellow* or *Calisaya* bark. Weddell gives the following as the characteristic properties of the bark:¹²¹—bitter coat, thin in the quills, almost smooth, very adherent, sometimes with traces of annular fissures, uniform dirty gray in color or marked with darker shades. Proper bark obscure yellow without, sprinkled with small brown spots when artificially denuded and marked with some shallow longitudinal wrinkles; obscure yellow and a little reddish within, coarsely fibrous and often rough to the touch. Transverse fracture short and corky exteriorly, without a resinous circle, inwardly with a few short, thick fibres. Flat pieces very dense, consisting about equally of bast and cellular tissue. Outer surface smoothish, sometimes slightly wrinkled longitudinally, ochre-yellow or more or less brownish, frequently marbled with grayish or silvery spots, the remains of the epidermis. Transverse fracture cork-like outwardly, short woody-fibrous inwardly. A freshly cut transverse surface shows inwardly rows of isolated, semi-translucent points, agglutinated in bundles, these being the sections of the cortical fibres. Longitudinal fracture almost without splinters. Epidermis of the large bark, when present, thin, unequal, sometimes warty, obscure gray in color, more or less brownish or greenish in spots. When scraped the bark sometimes shows deep brown spots. The warts mentioned are sometimes decayed and in falling off leave roundish depressions. Taste bitter, astringent, somewhat pungent. Ac-

¹¹⁹ Guibourt, *l. c.*, p. 160–161.

¹²⁰ Pereira, *l. c.*, p. 1630.

¹²¹ Weddell, *l. c.* p. 54, 56.

cording to von Bergen the bark somewhat resembles the fibrous Carthagena. Guibourt states that it was readily distinguished from the Calisaya by its more cylindrical form, its smoother outer surface, the remains of the white and fungous layer, the two shades of color, orange or brownish externally, and by its decoction not yielding a precipitate with sodium sulphate.

6. The bark of *C. micrantha* var. *rotundifolia* of Weddell:—The tree grows in Bolivia. The flat bark closely resembles Calisaya, whence it was probably used to adulterate the latter. According to Weddell, it was a bark of little density and consisted of the liber only, or of the liber and the cellular coating, the latter being generally semi-fungous in character and imperfectly exfoliated. External surface unequal, with superficial cavities similar to those of Calisaya, separated by irregular, corky elevations, but sometimes smooth from the presence of the entire cellular coating, bright grayish orange-yellow in color. Internal surface considerably fibrous, of the same color as the external surface, but brighter. Transverse fracture stringy, longitudinal fracture slightly splintery, dull on the surface. Taste decidedly bitter, quickly developed upon chewing, slightly pungent, but faintly astringent.

7. The bark of *C. amygdalifolia*:—Largely collected in Bolivia, and probably used to adulterate the Calisaya. According to Pereira¹²² it was imported alone or mixed with other barks, both quilled and flat. Differed from Calisaya by being less dense, more orange in color, having a cellular coat in the pieces deprived of the epidermis, showing a stringy transverse fracture, lacking annular fissures in the epidermis, and giving an astringent and but slightly bitter taste.

Under the name of *Yellow bark of Guayaquil* Delondre and Boucharlat describe a bark which occurred in very large rolls, brown in color much like that of Chinese cinnamon. The outer surface exhibited rather close but shallow longitudinal furrows and traces of white, very thin epidermis. Fracture exteriorly resinous, interiorly shortly fibrous. Taste strongly bitter, not astringent. The bark was rarely met with in commerce.

According to Weddell¹²³ a *false bark*, that is, one which was not

¹²² Pereira, *l. c.* p. 1629.

¹²³ Weddell, *l. c.* p. 63, 95.

derived from a *Cinchona* species, was sometimes mixed with *Calisaya*, which it resembled so closely as not to be distinguishable by the eye. The same authority states that it was obtained from *Gomphosia chlorantha*, a high tree growing in the same forests with the *C. Calisaya*. Its microscopic structure differed from that of the *Calisaya*. It yielded a volatile oil, which gave it a peculiar odor, and was totally lacking in alkaloid.

III. RED BARK.

Cinchona rubra.

Quinquina rouge.

China rubra, *rothe China*, v. Bergen.

China rubra, *Cortex chinae ruber*, Goebel.¹²⁴

Cascarilla roja verdadera, Laubert.

The term *red bark* is somewhat indefinite, for, as Pereira remarks, a red color is not characteristic of any one bark in particular but common to many, and appears not to be an essential quality, but to depend upon circumstances of locality, soil, age of the tree, and the mode of drying the drug. Thus, *C. lancifolia* yielded both a red and an orange-yellow bark, and Weddell found red tints in the barks of *C. ovata*, *C. scrobiculata*. *C. pubescens*, indeed even in *C. Calisaya*; and some of the red barks of commerce are scarcely distinguishable, so far as color is concerned, from the yellow barks. Nevertheless there appeared in the market, at some time near the beginning of the eighteenth century, a bark distinctly red both in the whole state and in the form of powder, which possessed certain qualities that distinguished it from the pale and yellow kinds; to this the name *red bark* or *true red bark* was specifically applied.

The introduction of *red bark* into Europe is stated by Dr. Saunders ('Observations on the Superior Efficacy, etc.,' 1782, quoted by Pereira)¹²⁵ to have taken place in 1702, when a Spanish vessel, taken by the English, was found to have on board a store of this bark, a portion of which came into the possession of Mr. D. Pearson, a celebrated apothecary of London. Another Spanish ship, bound from Lima to Cadiz in 1779, was captured by an English frigate and carried to Lisbon. The cargo consisted

¹²⁴ Goebel & Kunze, l. c., pl. 11, figs. 1-5.

¹²⁵ Pereira, l. c. p. 1641; Triana, l. c. p. 13.

chiefly of red bark, and was for the most part sent to Ostend, where it was purchased at a very low price by some London druggists. It was introduced into medical practice with some difficulty. According to von Bergen, red cinchona was already known in northern Germany at the beginning of the eighteenth century.

The species which produces the *red bark* was not known until after the middle of the nineteenth century. It was supposed for a long time that the *red bark* was derived from the same species with one or more of the pale barks, a notion which appeared to receive some support from the statement made by La Condamine¹²⁶ that three kinds of bark were known at Loxa,—the white, the yellow, and the red; that the white possessed hardly any medicinal virtues and was obtained from a tree entirely distinct from that which yielded the other two; and that he was assured that the trees producing the red and yellow grew together and were not distinguishable by the eye. From this it was inferred that the barks differed in color according as they had been collected from the trunk or from branches or twigs.

The notion was generally prevalent that the *red bark* was furnished by the *Cinchona oblongifolia* of Mutis.¹²⁷ This tree yielded a purple-red bark which was called *quina roja* or *quina Azahar o roja da Santa Fé*, and which was supposed to be the *red bark* of commerce; von Bergen, however, upon examining the *Azahar* bark in the collection of Ruiz found that it was not the commercial bark, but a *false cinchona* known to the French pharmacognosists as *quinquina nova*,¹²⁸ and Weddell found that the *Cinchona oblongifolia* Mutis was not a *Cinchona* but a species of his own allied genus *Cascarilla*, and he called it *Cascarilla magnifolia* var. *a vulgaris*.¹²⁹ The *Azahar* was also known as *Savanilla bark*. After the explosion of the *oblongifolia* hypothesis, Guibourt inclined to the view that the true red bark was the product of *C. Condaminea*, but later he attributed it to *C. nitida*. Weddell declared *C. ovata* var. *erythroderma* to be the mother plant. Then came the discovery, by Howard, in the herbarium of Sir W.

¹²⁶ La Condamine, *l. c.* p. 2.

¹²⁷ Pharm. Jour. XI, p. 321; Guibourt, *l. c.*, p. 123.

¹²⁸ Pereira, *l. c.* p. 1641; Goebel & Kunze, *pl. 11*, figs. 6–11.

¹²⁹ Weddell, *l. c.* p. 79.

Hooker, of a specimen of cinchona marked in the handwriting of Pavon, which he identified with the *red bark* of commerce; it proved the bark to be that of *Cinchona succirubra* Pavon, which Weddell had seen but not recognized, and which he had named the *erythroderma* variety of *C. ovata*. The researches of Sir Richard Spruce into the habit and geographic distribution of this tree have been referred to.¹³⁰ The *C. succirubra* in its habitat is a beautiful tree, attaining a height of 82 feet, and bearing leaves nearly 20 inches long and nearly 14 inches wide. Its distribution is somewhat confined. It is found on the western slopes of the Chimborazo (San Antonio de Huaranda), descending southward through Riobamba, Alausi, and Cuenca, to the province of Jaen in the department of Caxamarca, in northern Peru. The term *succirubra* described the property of its juice which, when the bark is wounded, exudes somewhat copiously, becomes milky upon exposure to the air, and quickly turns red in consequence of oxidation.

In South America *red bark* is called *Cascarilla roja* and *colorada*. It came into European trade from Guayaquil and Lima in chests. Pereira¹³¹ found good samples to be scarce. He gives the following description of the bark:—"In quills and flat pieces. The quills vary in diameter from two lines to an inch and a quarter; in thickness from one-third to two lines; in length from two to twelve or more inches. The so-called flat pieces are frequently slightly curled; their breadth is from one to five inches; their thickness from one-third to three-quarters of an inch; their length from two inches to two feet.

"Red bark is generally coated, and consists of liber, the cellular and suberous coats, and usually more or less of the epidermis; its outer surface is usually rough, wrinkled, furrowed, and frequently warty. The color of the epidermis varies; in the thinner quills it is grayish-brown or faint red-brown; in thick quills and flat pieces it varies from a reddish-brown to a chestnut-brown, frequently with a purplish tinge. As a general rule it may be said that the larger and coarser the quills and pieces, the deeper

¹³⁰ Spruce, R. Notes of a botanist on the Amazon and Andes. London 1908, II, p. 261, 273, 287, 407.

¹³¹ Pereira, I. c., p. 1641.

the color. Cryptogamic plants are not so frequent on this as on some other kinds of bark. The cellular coat is frequently thick and spongy, especially in large flat pieces, much more so than in yellow bark. It forms the round tubercles or warts. The inner surface of the bark is, in the quills, finely fibrous; in large quills and flat pieces, coarsely fibrous, or even splintery. Its color increases with the thickness and size of the pieces: thus, in fine quills it is light rusty-brown; in thick quills and flat pieces it is a deep reddish- or purplish-brown. Some of the specimens of red bark which I have received from von Bergen, as well as of those which I have found in English commerce, approach yellow bark in their color. The transverse fracture of fine quills is smooth; of middling quills, somewhat fibrous; of thick quills and flat pieces, fibrous and splintery. The taste is strongly bitter, somewhat aromatic, but not so intense and persistent as that of yellow bark; the odor is feeble and tan-like; the color of the powder is faint reddish-brown."

Guibourt¹²² classified the *red bark* in two principal varieties, the *quinquina rouge verruqueux* or warty, and the *quinquina rouge non-verruqueux*, or non-warty kind. He described also four other *red barks* as follows:—

1. *Rouge orangé verruqueux*, which differed from the true warty kind by having a more orange color, a very thin epidermis, fine fibres, and a less thickness in the large barks.

2. *Rouge blanchissant à l'air*, characterized by the fact that its fracture whitened in the air. It was but slightly bitter.

3. *Rouge de Lima*, which had a whitish epidermis, and an ochreous-reddish liber. It was a bark of excellent quality.

4. *Rouge pâle à surface blanche*. This resembled the first of these varieties but was distinguished by having a whiter epidermis and being generally lighter in color.

He also describes a *quinquina de Jaën ou de Loza rougeâtre*, with a gray epidermis and a uniform, fibrous liber, reddish or deep brown in color, and very astringent but little bitter in taste.

Early analysis of the bark gave very divergent results in the quantities of alkaloid present. Pelletier and Caventou, for example, found 1.7 per cent quinine and 0.8 per cent cinchonine.

¹²² Guibourt, *l. c.*, p. 126.

Riegel, of Carlsruhe, obtained 2.65 per cent quinine and 1.51 per cent cinchonine, a total of 4.16 per cent of these alkaloids; in another sample he found 3.85 per cent of both alkaloids. From the genuine "bright" red bark Delondre obtained 2 to 2½ per cent quinine sulphate and 1 to 1.2 per cent cinchonine sulphate; a "pale" red bark yielded 1.5 to 1.8 per cent quinine sulphate and 0.5 to 0.6 per cent cinchonine sulphate. The 'United States Dispensatory' of 1858 reports the highest percentages of cinchonine obtained to that time to have been 3.17 per cent, with 0.15 per cent quinine sulphate. Either the commercial barks varied considerably in their content of alkaloid or some of the analyses were reported on red barks other than the officinal kind.

CARTHAGENA BARKS.

Soon after the discovery of species of *Cinchona* in New Granada by Lopez, Santisteban, and Mutis and his pupils, the European markets were flooded with barks collected in those regions. The intense jealousy which this excited in the dealers in the Loxa barks and the tricks to which they resorted, according to Humboldt, in order to drive their competitors from the market, have been mentioned. The New Granada barks enjoyed some reputation for a time, and then, their inferiority to many of the other barks having become known, they were dropped from the officinal lists. However, with the establishment of the Bolivian monopoly in Calisaya bark—which led to its becoming known as *Monopoly Bark*—and the consequent deficiency of supply and high price of Calisaya, merchants again turned their attention to the barks of the north, especially as they could be used in the manufacture of the cinchona alkaloids. Within a few years large quantities of good bark were imported from New Granada, chiefly from the neighborhood of Bogotá and Popayan, and brought down on the Magdalena River. Transportation was facilitated by the completion of the railway across the Isthmus of Panama, by which considerable quantities of bark were brought down and shipped from the port of Buenaventura, on the Pacific Coast.

Under the head of *Carthagena Barks* were classified all those barks which originally came from the North Atlantic ports of South America. Commercially they were known variously as

Pitaya, *Bogota*, *Carthagen*a, *Maracaibo*, and *Santa Martha* barks, the names indicating the places where they were collected or the ports at which they were shipped.¹³³ Most of these barks were characterized by a soft, whitish or yellowish-white epidermis, possessing a peculiar micaceous appearance, which could be scraped easily by the finger nail. This epidermis was frequently removed before the bark was sent into the trade, but sufficient of it usually remained to indicate its character. In those commercial Carthagen a barks which lacked the epidermis, certain characteristic markings could be observed which showed that the exterior coat had been shaved or scraped off with a knife; these markings served to distinguish these barks from Calisaya, which some of them superficially resembled. All the barks of this class contained alkaloids, though they differed from one another in this respect. They yielded proportionately more cinchonine, cinchonidine, and quinidine than the Calisaya, in which they resembled the pale and red barks.¹³⁴

Certain *white barks*, so called because of the micaceous appearance of their epidermis, were derived from trees growing near the western coast of South America, and were of inferior quality. When they entered into commerce it was usually as adulterants of the better kinds. The 'United States Dispensatory' 1858, says that in the form of powder, they were formerly, and were still, sold to a certain extent in the shops for tooth powder under the name of *common bark*.

The Carthagen a barks were formerly specified as *yellow*, *orange*, *red* and *brown*; but this classification according to color meant nothing and was eventually abandoned. The Carthagen a barks which offered well-defined characteristics were the following. We choose the descriptions of them as given in the 'United States Dispensatory,' revised eleventh edition:—

1. *Hard Carthagen a Bark*, *Hard Yellow Carthagen a Bark*, *Yellow Bark of Santa Fé*, *Common Yellow Carthagen a Bark*, *China flava dura* von Bergen, *Quinquina de Carthagèna jaune pâle* Guibourt.¹³⁵—In pieces of various size and form, sometimes wholly

¹³³ Weddell, *l. c.* p. 75.

¹³⁴ Goebel & Kunze, *l. c. pl. 9, figs. 1-8*.

¹³⁵ Pereira, *l. c.* p. 1646.

or partially quilled, sometimes flat, the flat pieces presenting the appearance of having been warped in drying, being frequently curved longitudinally backward and sometimes also in transverse section or spirally. The quills from 3 to 8 lines in diameter, 1 to $1\frac{1}{2}$ line in thickness, and 5 to 9, rarely 15, inches in length. The flat pieces thicker, $\frac{1}{2}$ inch to 2 inches broad, and 4 to 8, sometimes 12, inches long. As found in the American market the bark was sometimes in small, irregularly square or oblong, flattish and variously warped pieces, 1 to 4 inches long, and 1 to 3 lines thick, mixed with small quills or fragments of quills; the former appearing as if chipped from the trunk or large branches, the latter evidently derived from the small branches. A bark was at one time described under the name of *St. Martha* bark, which was regarded as a distinct variety but later shown to be the one described, though collected in a different manner. The quills were generally more covered with the white epidermis than were the flat pieces in which it was often nearly or entirely removed. The inner surface of the latter, though sometimes smooth, was often rough and splintery, as if forcibly separated from the wood. The color of the proper bark was pale, dull, brownish-yellow, darker in parcels which had been long kept, and the surface often appeared as if rubbed over with powdered bark. The texture was rather firm and compact and the fracture abrupt without being smooth or presenting long splinters. The taste was bitter and nauseous. The bark was assigned to *C. cordifolia*.

2. *Fibrous Carthagenia Bark, Fibrous Yellow Carthagenia Bark, Spongy Carthagenia Bark, Bogotá Bark, Coquetta Bark, Quina naranjada* Mutis, *Quinquina orangé* Humboldt, *China flava fibrosa* von Bergen, *Quinquina Carthagène Spongieux* Guibourt:—This occurred in the form of quills or slightly rolled; there were comparatively few pieces which were quite flat, even among the largest barks. The quills were from half an inch to an inch and a half in diameter and of extremely variable length, with a yellowish-brown epidermis, often covered with crustaceous lichens so as to give the surface a whitish and smooth appearance, and exhibiting not infrequently longitudinal and transverse fissures. The larger barks, which were the kind most frequently encountered in commerce, were usually 6 to 12 inches long, from 1 to 2

inches broad, and from 2 to 5 lines thick, but they often varied much from these dimensions, being sometimes in the smallest fragments, and sometimes forming semi-cylinders 4 or 5 inches in diameter, a foot and a half long, and 9 lines thick. They were usually without the epidermis, which had been pared or scraped off with a knife, leaving the surface somewhat irregular in the former case and smooth and uniform in the latter. Sometimes the epidermis was present, wholly or partly, when it exhibited the micaceous appearance characteristic of the Carthagena barks. The bark was very fibrous, presenting generally, when broken, long, sometimes stringy, splinters, though the outer edge of the fracture was occasionally short from the remains of the suberous coat. The texture was loose, soft and spongy, and the bark generally was of a light weight. The color both of the trimmed outer surface and the inner surface of the bark itself varied from an ochreous- or light brownish-yellow to orange and red, but the orange predominated, which induced Mutis to call it *orange bark*. It was in the largest pieces that the red color was generally found. The larger pieces sometimes bore a deep spiral impression, the mark, probably, of a climbing plant winding around the stem of the tree. The powder was yellowish in color, not infrequently with an orange tint. The taste was more or less bitter, but the barks varied greatly in this respect, some having a decided taste while others were almost insipid. There was no doubt that these barks were all derived from the *C. lancifolia* of Mutis. It was asserted that the red variety of the bark was obtained from trees growing side by side with those that yielded the yellow or orange. A specimen labelled *yellow bark* of Loxa at one time reached the United States, having been brought from South America by Dr. Dillard of the United States Navy, who stated that it was employed in Loxa for making an extract. Its properties were so closely analogous to those of the fibrous Carthagena bark as to justify the supposition that it was derived from the same species of *Cinchona*. The authors of the 'Dispensatory' saw a specimen from Guayaquil which presented the same characteristics.

The 'United States Dispensatory' of 1843 described a bark of which large quantities had recently been imported into the United States by a vessel from Maracaibo. This bark bore a

close general resemblance to the *flat* Calisaya, particularly with respect to the inner surface, but it differed in being thicker, less hard, less compact, and less heavy and much more fibrous; the outer surface, too, appeared as if the exterior coat had been scraped or cut off with a knife and not separated naturally as is the case with Calisaya. The pieces were considerably larger than was usually the case with the fibrous Carthagena barks and differed somewhat in color also. In the outer portion some of the pieces were decidedly reddish. It was distinctly bitter, though less so than the Calisaya. Subsequent observation proved that this *Maracaibo* bark was to be ranked with the fibrous Carthagena barks.

Bogota bark, *Fusagasugá bark*, and *Coquito bark* were varieties, the first sent to Bogotá from the forests where it was stripped, the second collected at Fusagasugá. *Coqueta* (*Caqueta* ?)¹³⁶ bark occurred in English commerce, and is mentioned by Pereira,¹³⁷ but does not appear to have reached the United States, at any rate under that name. Its botanic origin, according to Pereira, was *C. lancifolia*. The bark known as *Bogotá* or *Fusagasugá* is described in the 'Dispensatory' as being in pieces of various length, often exceeding a foot, sometimes nearly flat but generally more or less rolled, and occasionally forming semi-cylinders more than an inch in diameter. It was either wholly or partly covered with the soft, whitish, micaceous epidermis. In other specimens the epidermis was removed by scraping or chipping, the deep stroke marks of the knife or hatchet being plainly apparent. The pieces were often of considerable thickness, were usually rather firm, very fibrous, and spongy under the teeth. The color was brownish-yellow with a tinge of red.

Soft Pitaya Bark, *Calisaya of New Granada* (Delondre et Bouchardat, 'Quinologie,' p. 33):—This bark was imported from Carthagena, to which port it was brought down the Magdalena River, and from Buenaventura, on the Pacific Ocean, reaching the United States from Panama. It was said to be collected in the Pitaya Mountains near Popayan. It appears to have been in quality superior to the other Carthagena barks. It came broken

¹³⁶ Pereira, *l. c.* p. 1644.

¹³⁷ Lambert, *l. c.* p. 83; Howard, *Pharm. Jour.* XI. p. 562.

up into small, irregular fragments or larger pieces, quilled, partially rolled or flat, few of the fragments exceeding four inches in length and some very small. Many of the seroons contained it in the state almost of coarse powder. The fragments were almost destitute of epidermis; when portions of it remained it exhibited the whitish, micaceous character peculiar to all the Carthagena barks. The outer surface, consisting of a thin, sub-epidermal suberous layer, was very uniform and smooth, probably due to careful scraping. The greater part of the bark consisted of the liber, which was very soft and highly fibrous, but easily broken. Both internally and externally the color was a uniform, fine brownish-yellow, with an orange tint and brighter than in most of the other barks. Its taste was very bitter.

3. *Hard Pitaya Bark, Pitaya Condaminea Bark* Pereira, *Quinquina brun de Carthagène, Quinquina Pitaya, ou de la Colombia, ou d'Antioquia* Guibourt:—This bark came sometimes from Carthagena, sometimes from Panama whence it was sent from Buenaventura.¹³³ It occurred generally in small, irregular pieces, from less than an inch to four inches long, representing the fragments of larger pieces, quilled and flat.¹³⁹ Pereira saw some pieces more than a foot long.¹⁴⁰ The pieces varied in thickness from less than a line to four or five lines, most of them being covered with the characteristic epidermis. Some of the pieces, however, had a dark brown epidermis, rugose with many cracks in all directions. Many others were partially or wholly destitute of epidermis, presenting generally, in the denuded part, a dark, uniform or wrinkled surface. The inner surface was finely fibrous, dull yellowish-brown in color with a reddish tinge, the whole of the liber having the same color and texture. In many places outside the liber occurred a distinct resinous layer, sometimes of considerable thickness, which, when cut across, exhibited a dark, reddish-brown, shining surface. This resinous layer is peculiar to the bark, though not present in all the pieces. The fracture was shortly fibrous toward the interior, often smooth toward the exterior. The whole bark was rather hard, compact and heavy.

¹³³ Weddell, *l. c.* p. 41, 75.

¹³⁹ Goebel & Kunze, *l. c. pl.* 12, *figs.* 6-7.

¹⁴⁰ Pereira, *l. c.* p. 1643.

The taste was very bitter. Its yield of alkaloids was considerable. The bark was collected in the mountains of Pitaya, near Popayan, from which the soft variety was also said to have come, being brought down on the Magdalena River. Pereira and Howard¹⁴¹ attributed it to *C. Condaminea* var. *pitayensis* Weddell, which was later made a distinct species called *Cinchona pitayensis*.

Pereira and Guibourt called the bark *Pitaya Condaminea*, and described it as follows:¹⁴²—"Bark consisting of single or double quills, or half-rolled pieces. I have specimens which are more than a foot in length. Some samples, however, which I have received, consist of pieces not more than two or three inches in length, sometimes entirely, at others partially, coated; the partially coated pieces consist of the suberous and cellular coats and liber. Epidermis, when present, dark brown, frequently coated by crustaceous lichens, marked by numerous closely set, transverse cracks, with prominent or slightly everted borders, which give the bark a grater-like feel; and here and there presenting round or oval warts, or fungoid, rusty tubercles, varying in size from a grain of wheat to a seed of coffee and usually marked like the latter with a longitudinal, sometimes also with a transverse, fissure. The suberous coat in some pieces much developed, spongy or fungous, fawn-yellow, sometimes brown in the interior and yellow externally and internally. Resinous tissue on the inside of the suberous coat, from which it is definitely separated, shining, of a dark reddish-color. Liber gradually passing into the resinous coat, hard, dense, dark reddish-brown; cortical fibres small and short. *Pitaya Condaminea* bark is firm and heavy, and has a very bitter, rather disagreeable taste, which is slowly developed."

With the introduction of the cinchona trees into Java and British East India and their successful cultivation there, the importance of South America as a cinchona-producing country declined. To-day about nine-tenths of the bark is derived from Java, where the *Cinchona Ledgeriana* receives special attention. The cultivation of this species has also been introduced into India and Burma, where it thrives on the government plantations. The

¹⁴¹ Pereira, *l. c.* p. 1644.

¹⁴² Pereira, *l. c.* p. 1643; Guibourt, *l. c.* p. 96.

chief species now yielding commercial barks are *C. Ledgeriana* Moens, *C. Calisaya* Weddell, *C. officinalis* Linné, and *C. succirubra* Pavon, besides a number of hybrids. The *C. lancifolia* of Mutis, and other species are, however, still occasionally imported from South America for the purpose of manufacturing cinchona alkaloids other than quinine. In fact, the recognition of the medicinal value of cinchonine, cinchonidine, and quinidine has led the British Government to turn its attention to *C. succirubra*, which was comparatively neglected because of its lower quinine content, and in India it is now replacing to some extent the *C. Ledgeriana*. The dreams of Hasskarl and Markham have been realized far beyond their expectation.

FALSE CINCHONA BARKS

A few words must be said respecting a number of barks which so closely resembled the Peruvian febrifuge as to be believed to be derived from species of the genus *Cinchona*. Some of these appeared to have possessed febrifuge properties, indeed, but investigation proved that they were devoid of the peculiar cinchona alkaloids. Of these barks the following were the most common:

*Quinquina nova*¹⁴³ as it was called by the French pharmacists, or *new bark*.—Guibourt showed that it came from the *C. oblongifolia* of Mutis, a species, as has been stated, that does not belong to the genus *Cinchona* and whose bark is worthless. It was at one time called also *red Carthagenia* bark.

Caribbean Bark, from an *Exostemma*.

St. Lucia Bark, called by the French *quinquina piton*, from *Exostemma floribunda*.

A bark called in France *quinquina bicolore* and in Italy *China bicolorata*.—It was also sometimes called *Pitaya bark*. The 'United States Dispensatory,' 11th edition, states that a considerable quantity of this was at one time imported into New Orleans, whence it reached Philadelphia. Its botanic origin is unknown.

Many other species of plants formerly regarded as belonging to the genus *Cinchona* but later shown to be of other genera were of botanical interest but of no importance to the pharmacognosist.

¹⁴³ Goebel & Kunze, *l. c.* pl. 11, figs. 6-11.

ADDENDUM

The origin of the name *quina quina*, at one time used for the tree yielding the fever bark, and transformed by the French into *quinquina* and by the Germans into *China China* or simply *China*, has not been satisfactorily explained. It is undoubtedly of South American origin and became prevalent in Europe, but was not used in Loxa, according to La Condamine, for the tree now called the *Cinchona*. There grew in South America, however, a tree which the natives called *quina quina* and which, according to the description given of it by La Condamine, was in all probability the one yielding the Peruvian balsam. Our older dispensatories and textbooks, Pereira, for example, call it *quinquino*. How, then, did the name of the balsam tree come to be applied to the cinchona? La Condamine offers a conjecture:—

Parmi les différentes vertus qu'on attribué à l'arbre balsamique dont nous venons de parler, & nommé de tout temps *Quina Quina* par les Naturels & depuis par les Espagnols, la plus considérable est celle de son écorce, qui passoit pour un excellent fébrifuge. Avant la découverte de l'arbre de *Loxa* cet autre étoit en grande réputation pour guérir les fièvres tierces, & les *Jésuites de la Paz* ou *Chuquiabo* recueilloient avec grand soin son écorce, qui est extrêmement amère, et étoient dans l'usage de l'envoyer à Rome où elle se distribuoit sous son vrai nom de *Quina Quina*, et servoit contre les fièvres intermittentes. L'écorce de *Loxa* ayant passé en Europe et à Rome par la même voye, le nouveau fébrifuge a été confondu avec l'ancien, et celui de *Loxa* ayant prévalu, il a, retenu le nom du premier, qui est aujourd'hui presque entièrement oublié; le nom de *Cascarilla* ou de petite écorce, donné à celle de *Loxa*, semble aussi avoir été imposé pour la distinguer d'une autre, qui étoit sans doute celle de l'ancien fébrifuge.

Badus a confondu les deux arbres faute d'avoir eu connoissance de l'ancien, ce qui fait qu'il ne peut concilier le témoignage de son Auteur Génois avec d'autres relations. *Praeter corticem*, dit *Badus*, *sunt qui dicunt inesse eandem virtutem, fugandis febribus semini arboris illius, quod patrio sermone seu Hispano dicunt Pipitas de Quina; estque simile, aiunt, semini Cucurbitae . . . non convenit cum eis Bollus, qui ait arborem sponte sua nasci, negatque insuper inesse ei fructus ullos . . . Addit idem Bardis, resinam quoque inesse arbori seu cortici, nescio an sit supparis virtutis cum cortice et illo semine.* Bad. Anast. Cort. Per. cap. 1.¹⁴

With respect to the etymology of the word La Condamine criticizes a derivation given by Don Diego de Herrera (d. 1712) in an unpublished manuscript entitled 'De Cortice Quinae Quinae et de Loxa, etsi diversorum arborum uniformis virtutis,' which he discovered in the pharmacy of the college of Jesuits of St.

¹⁴ La Condamine, l. c. p. 12.

Paul de Lima, after which he advances his own hypothesis. He says:—

Quant à l'étymologie du nom *Quina Quina*, ce même Auteur en propose une peu vraisemblable, donnant à entendre que les semences de l'arbre balsamique ainsi appelé, peuvent avoir reçu ce nom de la ressemblance qu'elles ont avec des playes ouvertes, telles qu'elles sont représentées dans l'E'cusson de Portugal au nombre de cinq, sous le nom de *Quinas*. Cette origine paroît non-seulement forcée, mais ne peut s'accorder avec un fait avéré & dont l'Auteur même convient, qui est, que le nom de *Quina* est de l'ancienne langue du Perou; cependant aucun de ceux que j'ai consultés à *Lima* & ailleurs, les plus versés dans cette langue, n'a pu me dire ce que signifioit en cet idiome, le mot *Quina*. J'ai trouvé dans un ancien Dictionnaire de la langue *Quichoa*, c'est ainsi qu'on nomme celle des anciens Perouans, du temps des *Ingas*, imprimé à *Lima* en 1614, le mot *Quina ai* aujourd'hui hors d'usage & inconnu des Naturels mêmes du pays, dont la langue s'est fort altérée par le mélange de l'Espagnol, ce mot est traduit dans le Dictionnaire par le mot Espagnol *Mantelilla India*, espèce de mante ou de cape dont s'enveloppoient les Naturels. Comme la langue *Quichoa* est fort peu abondante en termes, & que pour suppléer à cette disette elle n'a gueres de mot dont la signification ne s'étende par métaphore à diverses autres, on peut présumer avec assez de vrai-semblance, que *Quina ai*, qui s'entendoit ordinairement d'un manteau, pouvoit aussi signifier écorce quand il étoit question d'un arbre, ou du moins, avoir eu anciennement cette signification; je compte pour rien la petite différence dans la terminaison si ordinaire aux mots qui passent d'une langue à une autre; si cette étymologie est goûtée, il n'y aura plus de difficulté dans la répétition de *Quina Quina*, cette sorte de reduplication étant fort familière à la langue en question, & particulièrement dans les noms de Plante; c'est ainsi qu'ils en nomment diverses autres par des noms ainsi redoublés, comme *Vira Vira*, *Pinco Pinco*, *Saya Saya*, *Moco Moco*, donnant à entendre par ce redoublement une plus grande vertu, ou une plus grande efficacité dans la Plante. Supposé donc que *Quina* signifîât écorce en Indien, *Quina Quina* voudrait dire l'écorce par excellence, ou l'écorce des écorces.¹⁴⁵

In the note of Jussieu's quoted in the beginning of this monograph, referring to the Jesuit who was cured of a fever by a cacique, it is stated that the Father, regarding the bark of the balsam tree as identical with that which had relieved him, took both to Europe. Tschirch declares that both Jussieu and La Condamine were in error, as the bark of the balsam tree bears no resemblance whatever to cinchona, that it has the odor of coumarin and an astringent but not bitter taste. Moreover it remains to be proved that *quina* in the Quichua language means "cloak" or "bark." The oldest names for cinchona among the natives of South America were *Guananepide*, *Guannoneperide* and *Chinenepide*. The Spaniards designated it *palo de calenturas*,

¹⁴⁵ La Condamine, l. c. p. 13.

leño de calenturas, and *lignum februm*. European physicians and apothecaries abandoned the reduplication of the *quina* and wrote the name *China de China* or simply *China*.

As in the case of *quinaquina* or *quinaquina*, so is the derivation of the term *Calisaya* still an open question. It was at one time generally supposed that it was the name of a Bolivian province in which the bark was collected; but there is no such province in Bolivia, though Humboldt states that there is one in southernmost Peru in the intendencia de la Paz. A few derivations of a more or less fanciful character have been given. Laubert and Pöppig derived it from *colla*, a remedy, and *salla*, stony ground. Weddell refers its origin to *colli* and *saya*, both Quichuan words, the former meaning *red*, the latter *sort*.¹⁴⁶ These names, he thinks, were given in reference to the red color assumed by the denuded surface of the bark upon drying, or perhaps to the red color sometimes assumed by the leaves. It may be remarked that in South America the name was generally spelled *Colisaya*. Markham, finally, thought that the name might have some connection with a family named *Calisaya* who are said to have taken some important part in the affairs of the province of Carabaya on 1780.¹⁴⁷

In conclusion we may give the names given to the bark in the more important of the modern languages:

In the pharmacopoeias, *Cortex cinchonae*, *Cortex peruvianus*, *Cinchona*.

German, *Fieberrinde*, *Chinarinde*.

Dutch, *Kinabast*.

English, *Cinchona Bark*, *Peruvian Bark*, *Bark*.

French, *Ecorce de quinquina*.

Italian, *Corteccia di china*.

Spanish, Portuguese, *Quina*.

Swedish, *Feberbark*.

Serbian, *Kina*.

Russian, *Chinna ja Korka*.

¹⁴⁶ Weddell, l. c. p. 31.

¹⁴⁷ Markham, l. c. p. 58.

THE CHEMISTRY OF CINCHONA, HISTORICALLY CONSIDERED

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Paracelsus, the great reformer of medicine and chemistry, had breathed his last almost a century before, when cinchona bark made its debut to European science and society as the remedy which had saved the life of the Countess of Chinchon, the wife of the viceroy of Peru. The battle between the galenists and iatrochemists was being fought even more fiercely, if that were possible, after the death of the medical iconoclast than during his life time. On the one hand, the orthodox physician had to fore-swear the internal use of chemical remedies; on the other hand, the Thirty Years War, with its concomitant demoralization of all classes of society, had turned some of the wholesome practices of Paracelsus into the channels of quackery. Of the three centuries—from the Renaissance, signalized not only by the rebirth of classical learning but by remarkable geographical discoveries, by the art of printing with individual type, and last, but not least so far as our subject under consideration is concerned, by the birth of pharmaceutical chemistry, up to the chemical revolution led by Lavoisier, himself a victim of the contemporaneous French political, economic and social revolution—the first half is known to chemical historians as the iatrochemical period, the second half as the phlogistic period. Many, if not most, of the principal representatives of the former period were physicians (Paracelsus, Mayerne, Libavius, Sala, Van Helmont, Sylvius, and Tachenius); those of the latter period were in no small part apothecaries (Lemery, Neumann, Marggraf, Geoffroy). The discovery of the medicinal use of cinchona by Europeans falls toward the end of the iatrochemical period, or the middle of the qualitative period, a term applied to the joint periods previously mentioned (the period of “*Neue Geschichte*” of German historians) as distinguished from the quantitative period of chemical history (contemporaneous with the “*Neueste Geschichte*” of continental historians). True, the continental apothecaries had not remained untouched by the chemical and medical revolutions which they

were experiencing between 1500 and 1650. But, in like manner as most medical practitioners were slow to leave the ranks of the galenists, so the apothecaries were slow to break with pharmaceutical traditions of the past. In this respect we may witness a like conservatism in the representatives of modern chemistry who to-day cannot discard such concepts as acid, base, and salt, which have greatly retarded chemical thought for more than half a century and which should have been obsolete long before our day.

We are not surprised, therefore, that cinchona was dispensed largely, if not entirely, as a powder. Even to-day we have with us such specimens of pharmaceutical terminology as Powder of the Countess (with reference to the Countess of Chinchon), Jesuits' Powder (because the Jesuits were shrewd enough to make propaganda by its distribution), and lastly Cardinal's Powder (because the Jesuits had sent a lot of the powder to Cardinal Lugo in Rome). My good friend, Otto Raubenheimer, is of the opinion that history of pharmacy should be taught pharmacy students, partly, at least, to acquaint them with these and other historical specimens of pharmaceutical terminology. These terms remind us of that period of the history of pharmacy when one of the principal occupations of the apothecary was to wield mortar and pestle—even to-day the symbol of the art of pharmacy as the urinal is that of the art of the physician—for the purpose of converting barks and roots into a powder, thus rendering them more easy of administration, or to mix these powders with honey or sugar syrup so as to make them more palatable.

The average student of pharmacy to-day thinks of tinctures and extracts as modes of administration of the galenical school of the healing arts, yet they were introduced by the Paracelsists, as were the distilled waters and spirits, which were supposed to represent the quintessence of the drugs from which they were prepared. Extraction and distillation were regarded as distinctively chemical operations. Like the infusions and decoctions of the older school, the extracts of the iatrochemical school were prepared from the "bark," i. e., the bark above all other barks, the bark par excellence. Jacobus le Mort, however, does not mention tinctures or extracts of any kind in his 'Pharmacica' of 1688, al-

though the orthodox galenists accused him of medical heresy.

Lemery, in his 'Cours de Chimie,' directs the preparation of a vinous tincture as well as that of an aqueous extract, the latter of the consistency of honey. The former is directed to be prepared in the following manner: "Schuettet in eine Cucurbit vier Untzen gute und grobhin gepulverte Chinam de China, giest Spiritum Vini drauff / biss er 4. Finger hoch ueber die Materie weggeht / thut noch eine andere Cucurbit darueber / dass ein Vaisseau de recontre herauskomt: verlutirt die Fugen mit allem Fleiss / und stellt euer Gefaess 4. Tage lang in einen Mist oder Balneum vaporum: ruehrets nach und nach mit umb / so wird der Spiritus Vini eine rothe Farbe bekommen / macht die Gefaesse auff / filtrirt die Tinctur durch Loesch-Pappier / und hebt sie in einer wohlverwahrten Flasche auff." (German edition of 1698, part II, p. 35.)

In his 'Elémens de Pharmacie' of 1762, Baumé gives directions for the preparation of an aqueous *Extrait Sec de Kinkina*. In the new edition of 1818, revised by Bouillon-Lagrange, this preparation is classed with the *extraits gommeux-resineux* and the word is spelled *quinquina*. In his 'Prix Courants des Préparations de Chymie et de Pharmacie' of 1775, Baumé enumerates an *Extrait de quinquina à l'eau* at 32.1 per pound, and an *Extrait de quinquina au vin* at 36.1 per pound; also a *Teinture de quinquina* at 4.1 per pound. When Trommsdorff wrote his 'Handwoerterbuch der Pharmacie' in 1809, he mentions that, "A good bark yields one-fourth of its weight of aqueous extract, and approximately one-eighth of resin." This characterization reflects the chemical evaluation, as it were, of this important drug little more than a century ago, the precursor to our more modern alkaloidal assay.

Although Bergman had begun to "distinguish organic from inorganic bodies" about 1780, and although Woehler, in 1828, had "synthesized" urea, thus obliterating the distinction between organic and inorganic, Berzelius in 1838 still maintained the older classification of the *materia chemica*, in accordance with the three natural kingdoms, into mineral, vegetable, and animal ('Lehrbuch d. Chemie' 3te Ausgabe, translated by Woehler) as Lemery had done more than a century and a half before ('Cours de Chimie,' 1675). True, in Lemery's 'Cours de Chimie' vege-

table chemistry corresponds, so far as contents are concerned, more to a modern treatise on vegetable pharmacognosy than to a text on chemistry. About half a dozen definite organic chemical compounds are enumerated, viz., sugar, camphor, flowers of benzoës, etc. In Berzelius' 'Lehrbuch' the ratio of crude vegetable drugs to organic chemical compounds has greatly changed in favor of the latter. However, the treatment of drugs has not changed materially. Thus in his monograph on Cinchona, in the chapter on barks, he reports the results of an analysis made by himself ten years before the discovery of quinine by Pelletier and Caventou (1820):

A green, soft resin which soon hardened.....	0.5
Tannic acid plus its "Absatz" (phobaphene?).....	7.35
Bitter extract of syrupy consistence.....	6.87
Impure quimates of potash and lime.....	2.5
"Extractabsatz" extracted from the wood by means of carbonate of potash.....	1.25
A starch-like gum subsequently extracted with boiling water...	2.7
Wood fibre.....	73.75
Loss.....	5.08

(*Ibid.* vol. VII, p. 396). Such were the results of a chemical analysis made a little more than a century ago by one of the foremost representatives of chemistry of all times.

All of this, however, was changed when, in 1820, Pelletier and Caventou, two French pharmacists, isolated quinine and cinchonine. Just as the so-called "wet method," applied by Scheele to the isolation of benzoic acid, had led to the discovery of a number of vegetable acids in rapid succession; so the recognition of the basic, salifiable properties of morphine by Sertuerner led to the discovery of a number of alkaloids. The first decade after 1817 witnessed the isolation of not less than fourteen alkaloids. Among these were quinine and cinchonine. However, this was only a beginning, for the cinchona barks proved a veritable mine of this new type of organic substances. Quinine, discovered in 1820, appeared in the fifth edition of Magendies' 'Formulaire . . . de Nouvelles Medicamens' of 1825.¹ Other quinine alkaloids and their salts were introduced into the new *materia medica* in rapid succession. What is even more remarkable, the use of this new item of the physician's armamentarium spread rapidly. Thus

¹ Earlier editions were not available, hence not consulted.

it is a matter of record that in 1835, when Milwaukee had not even been incorporated as a village, quinine was being dispensed by a Dr. Chase. Apparently, however, he was somewhat timid about its use, for the following story is told about him. "His favorite remedy for fever was calomel, administered in heroic doses. At that time quinine was just beginning to come into use and it is related that on one occasion he gave what he supposed to be twenty-five grains of calomel to a woman, but soon afterwards discovered that he had given quinine by mistake. With considerable anxiety he awaited the consequences and was agreeably surprised when the fever disappeared and the patient rapidly recovered." What is even more significant, the 'Milwaukee Sentinel' a few years later, contained an advertisement announcing the receipt by one of the early druggists, of a considerable quantity of quinine sulphate. An advertisement of 1843 announces the receipt of not less than two hundred ounces.

If quinine sulphate found its way into our unsettled western territories in such quantities at so early a date, its manufacture and that of the other salts must have been considerable even in the first decades after the discovery of this alkaloid. As a result, by-products must have accumulated in large amounts. It is reported that in 1826, six years after the discovery of quinine, Pelletier and Levaillant manufactured 177 ko. of salts of the alkaloid from 1593 cwt. of bark. In 1901 there were stored in a single port, Amsterdam, more than ten million pounds of cinchona bark to be converted into this panacea against fever. That the by-products referred to should have aroused the interest of the chemist as well as of the therapist need but be mentioned. As a result the following alkaloids were isolated in the order enumerated.

1820. Quinine. Pelletier and Caventou.

1820. Cinchonine. Pelletier and Caventou (Schmidt, Ph. Chem. II, p. 1564).

1846. Quinidine. van Heijningen (Schmidt, Ph. Chem. II, p. 1561).

1847. Cinchonidine. Winkler (*ibid.* p. 1570).

Homocinchonidine. Hesse (*ibid.* p. 1573).

Quinamine. Hesse (*ibid.*), and others.²

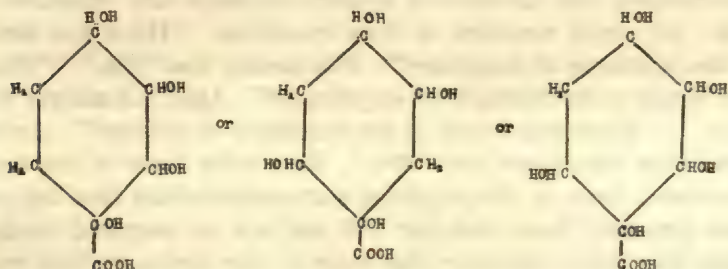
² See also "Minor Alkaloids of Cinchona Bark." by Mr. Frederic Rosengarten.

If it was the discovery of the basic, salt-forming properties of morphine, observed by Sertuerner in 1817, that led to the recognition of the plant bases or alkaloids, i. e., alkali-like substances, a discovery made in 1842 in connection with quinine was to lead to a chemical definition of this important class of plant chemicals.

It was in this year that Gerhardt obtained a basic compound, which he named quinoleine, by distilling quinine (also cinchonine and strychnine) with potassium hydroxide. In the following year Hofmann identified this with Runge's leukol which had been obtained from coal tar. Woehler then substituted the word quinoline. The isolation of pyridine and quinoline, the latter a condensed pyridine-benzene nucleus, led Wischnegradsky and later Koenigs to the conception of alkaloids as pyridine derivatives. This definition not only excluded mercurialine, identified by Ernst Schmidt as methylamine, but also all of the purine bases, viz., caffeine, theobromine, theophylline, from the concept alkaloid. Even after it had been shown that many of the alkaloids proper were not closely related to pyridine and quinoline, if at all, Pictet as late as 1904 based his treatise on a definition which rested on the formation of quinoline from quinine at high temperatures and under the influence of a strong chemical reagent.

Interesting as is the chemistry of the cinchona alkaloids, they constitute but 4-7 per cent of the dried bark. It was assumed by De Vrij that, in part at least, the alkaloids are combined with a tannic acid, namely cinchotannic acid. Moreover, in the living plant the tannic acid is supposed to be combined with sugar, hence quinine and its associates are assumed to be present as a complex alcaloido-tanno-glucoside. Although the constitution of quinine and glucose are known, that of cinchotannic acid has not yet been revealed, hence that of the complex is unknown. If the constitution of cinchotannic acid is complex—according to Schuett the empirical formula reveals no less than forty-three carbon atoms ($C_{43}H_{50}O_{20}$)—the constitution of one of its oxidation products, cinchona red, a so-called phlobaphene, is even less understood. Tschirch points out that cinchona red is an oxidation product of cinchotannic acid, resulting from the action of an oxidase. This observation may throw light on the older classification of cinchona barks into gray, yellow, and red.

Quinine, quinidine, cinchonine, cinchonidine, etc., cinchotannic acid, cinchona red, quinoline, are chemical terms derived from *quina*, the name of the tree, and *cinchona*, after Chinchon. There has been isolated from the bark still another chemical unit which derives its name from the tree, viz., quinic acid. This is a tetra hydroxy hexa hydro benzoic acid that is of particular interest to the plant physiologist and plant chemist because of its intermediate position between the sugars and aromatic acids of the benzoic acid type.



Besides occurring in cinchona barks up to 9 per cent, it is found in other plants, among them the sugar beet. It is closely related to the monocarboxyl quercite and to shikimic acid, intermediate compounds between the aldoheptose type of sugars and aromatic acids. It is noteworthy that it is a sugar of the little known aldoheptose type and not one of the much better-known hexose types that bridges the chasm between the aliphatic and aromatic constituents of plants.

Interesting as might be a discussion of the revelation of the structure of so complex a molecule as quinine before an audience of organic chemists, this is not the place to indulge in such a dissertation. Neither are place nor time opportune to indulge in a recitation of numerous other chemical substances that have been isolated from cinchona species, such as a phytosterol, starch, sugar, calcium oxalate, and even traces of copper. Suffice it, in closing, to point out that our knowledge of the chemistry of the genus *Cinchona* is restricted almost entirely to the constituents isolated from the bark. Grateful as we are to the quinine industry for having made available to the plant chemist minor constituents

in considerable quantity, it seems a pity that biochemical considerations have received attention only so far as they were incidental to making useful by-products that resulted in the production of quinine for the market.

A number of years ago the business manager of the University of Wisconsin, by profession a zoologist, queried the advisability of the establishment of a pharmaceutical garden in an age when the "Farbenfabriken" of the "Fatherland" produced artificially from coal tar not only the innumerable dyes rivaling the colors of the rainbow, but the host of modern synthetic new remedies as well. My reply consisted of three questions. "Have you heard of the synthesis of morphine?" His answer was "No." "Have you heard of the synthesis of strychnine?" Again his answer was "No." "Have you heard of the synthesis of quinine?" And a third time his answer was "No." Here were three of the most important items of the physician's armamentarium that had not been prepared from coal tar and are not so prepared to-day. Since then plant chemistry has come to the fore more than ever.

Though a pharmaceutical chemist by profession, far be it from me to see in the isolation of medicinal chemicals from plants—important as that may be—the only, or even the principal, object of phytochemistry. Coal tar may yield another hundred thousand synthetics, but what of plants? According to Wehmer, 'Die Pflanzenstoffe,' the phytochemist's "Beilstein," a small fraction of one per cent of the known plants has been touched upon chemically. Of these the peppermint, to take a technologically important example, has been studied chemically for more than a century and a half, in other words ever since modern chemistry had its beginning. True, chemists have revealed no less than thirty-five distinct volatile chemical compounds. Please note the attribute volatile. Now the sum total of the volatile constituents of peppermint constitutes about one per cent of the dried plant. Of the remaining ninety-nine per cent, with the exception of such widely distributed substances as cellulose and chlorophyll, we knew next to nothing until a few years ago.

The same situation prevails to no small extent in connection with cinchona. To be sure, we know something about a larger percentage of the constituents of the bark, but the study of the

leaf, this complex of innumerable microscopic laboratories, the cells in which the plant manufactures the numerous compounds that go into the building up of the stately tree, has been sadly neglected thus far. Biochemically, therefore, we still have much, very much indeed, to learn about this interesting genus of plants.

THE MEDICINAL USE OF CINCHONA

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In order to appreciate the value of cinchona as a remedy, it is necessary to know something of the disease for which it is still chiefly used and for the cure of which it obtained its renown.

Intermittent fevers have the widest geographic distribution of all infectious diseases. Most numerous and most severe in the tropics, they flourish to the sixtieth degree of North latitude in the eastern hemisphere, and the forty-fifth in the western. Careful statisticians estimate that eight hundred million people are constantly affected by some form or other of intermittent fevers, and that two millions die every year as the result.

On account of their striking symptoms, they can be traced back with more accuracy than most diseases to the earliest medical writings. The ravages of these fevers in Greece in the World War confirmed the opinion of many students of disease that intermittent fevers were important causes of the decadence of ancient Greece, just as the tenacity with which they still exist in modern Italy points to them as important causes of the economic and cultural decline of imperial Rome. They affect all times, all races, and all nations—Caucasians most severely, dark races least, but the blacks and browns often act as carriers, whole populations being infected, not severely enough to incapacitate them, but enough to set up new infections when they come near susceptible people and the proper species of mosquitoes. So it was that Hannibal's African mercenaries set up epidemics in Italy, just as negroes from the southern states now bring parasites to northern cities where lakes and casual water furnish breeding places for anopheles mosquitoes.

The chief characteristic of these fevers is their intermittent course, with paroxysms lasting nine to twelve hours in the milder forms and up to forty hours in the malignant tropical forms, which may develop far beyond the tropics if tropical heat is present for even a short time. Called ague at a very early period on account of the acute fever, that term was soon applied to the more conspicuous feature, the chill, with shaking of the body, in

common language, "ague shakes." Beginning with a feeling of chilliness and with shivering, violent shaking follows. The temperature rises even during the chill, and soon can be felt as a burning heat all over the body, with thirst, nausea, and vomiting, pains in muscles and bones, headache, delirium, and other symptoms. After some hours the fever subsides, followed by profuse perspiration, after which there is a stage of relative well-being, the intermission or remission, according to the degree of freedom from symptoms. If untreated with cinchona preparations the paroxysm returns the next day, or the third or fourth, each attack true to its type, although combinations may occur, with attacks every day or even twice in twenty-four hours. Similar symptoms sometimes occur in other diseases, especially typhoid fever, septicemia, and pyemia (endocarditis), tuberculosis, etc., but are easily distinguished by the blood examination.

Technical names for the types, quotidian or daily, tertian or every other day, and quartan, every fourth day, were applied very early and became so familiar that they passed into every-day use, as may be seen in the English of Chaucer, and of Shakespeare, who has Mrs. Quickly tell of Sir John Falstaff's "burning quotidian tertian."

Like all infectious diseases, intermittent fevers may assume epidemic proportions, and they have done so in many times and places, notably Greece, Italy, and Central America, and in the pioneer days in the Middle West. Disabling and often fatal in individual cases, intermittent fevers have long been recognized as potent causes of race degeneration, leading to stunted growth, loss of energy, and early death. While the acute attacks may subside spontaneously, they are prone to relapse, and from repeated attacks the subjects become anemic and dyspeptic, with enlarged spleen and liver and general malnutrition. Even now in hot countries, notwithstanding the advances in sanitation and treatment, intermittent fevers are responsible for the greatest percentage of illness, although the direct death rate may not be high. When neglected, as they often are in poor and ignorant populations, the working capacity and duration of life are markedly reduced. The shorter average life up to recent times was largely due to the effects of these diseases, and similar condi-

tions can still be seen in the white stock in many tropical countries. So in Transvaal the school children show physical degeneration as the result of ague, and one-third of juvenile criminality, with psychoses, is referred to it.

So striking a disease early made men seek a cause operating from outside the body, and not changes in the humors, the accepted explanation for diseases in general for hundreds of years. Some early myths relate to death-dealing monsters in marshes, and some of the feats of Hercules and Apollo probably refer to prehistoric works undertaken to drain such places. The engineering skill of the Italian race is shown in very extensive tunnels evidently made for drainage purposes. Even before our era the relations of drainage to health were impressed on city builders and dwellers on land alike. Lucretius, Vitruvius, and Columella all recognized the harmful effects of marsh emanations, and the Roman encyclopedic writer Varro (116–27 B. C.) in his *'Rerum Rusticarum,'* suggested that minute animals living in marshes might be the exciting causes of fever. Similar ideas were taken up again at various times and places, but could not overcome the fixed belief in alterations of the so called humors as disease factors. In Italy the belief in vitiated air gave rise to the popular term "*mal'aria*," so expressive that it early became incorporated into formal speech and even in technical language (Torti, 1753). It was brought to England by Horace Walpole in 1740, and became so familiar it was used metaphorically by Southey and others—"moral malaria," "malaria of infidelity." Proposed as a medical term by John Macculloch in 1827, it was urged as a general explanation of many and various diseases and so gave rise to a routine and careless diagnosis and treatment that continued down to the end of the nineteenth century. In spite of the efforts of linguistic purists "*malaria*" has now become adopted everywhere for the name of the disease.

After many fruitless efforts to find the suspected germ by investigators in various countries, the task was accomplished in 1880 by Alphonse Laveran, a French army surgeon stationed in Algiers, and his findings fully confirmed in the next five years. Towards the end of the century the role of the mosquito in transferring the parasites by way of their salivary glands was made

clear by the labors of Ronald Ross, the younger Manson, Big-nami and Grassi, and thoroughly confirmed wherever malaria occurred. This cleared up a great difficulty in the previous studies of malaria, the contradiction between the obvious participation of marshes and the occurrence of infections in places not at all marshy and even apparently healthy. As the anopheles mosquitoes can breed in casual water, such as in broken bottles, tin cans, roof gutters, and fountains, the necessity for gross marshes disappeared. We now explain intermittent fever as the result of an invasion by minute animal parasites, protozoa. The difference between this explanation and the older ones is as great as that between the idea of the earth as a flat disc or as a sphere. For example, Galen, whose authority was so great for centuries, thought quotidian fever was caused by mucus, tertian by bile, quartan by black bile, an imaginary secretion of the spleen. The intermittence was a feature that led to much speculation and arrested the attention of some of the most intelligent men. Thomas Dover, inventor of the well-known powder, thought it must come from the brain. Erasmus Darwin compared the alteration of symptoms to sleeping and waking. Others referred the changes to the rotation of the earth, the influence of the moon, the upright and horizontal positions of the body. It was not until the cycle of symptoms was proved to be due to the stages in the life of the parasites, and the digestion by the latter of the red blood corpuscles in or on which they live, that the intermissions could be explained. The length of the cycle depends upon the species of parasites, the tertian forms reproducing in about forty-eight hours, the quartan in about seventy-two. The time being not precisely multiples of twenty-four hours, a paroxysm may come earlier or later in the day than the preceding one.

It was only after these facts were made known that the treatment could be directed to the cause, although the specific was used long before this was known. How it came into being must now be considered. Up to the middle of the seventeenth century malarial fevers were treated like all other diseases, either for details of symptoms, such as chill, high temperature, or on various theoretical grounds including the position of the planets. For example, vomiting was a common symptom in the attack and was

considered an effort on the part of the body to cast out the poison of the disease, and accordingly the patients were drenched with emetics. Usually also they were given various drugs to prepare the system for still other drugs, to correct a supposititious error of body fluids, and for other reasons difficult for us to understand. We can understand the fact that patients were kept sick for weeks before beginning what was considered the final treatment. There was a long time when men questioned "whether they might safely attempt to cure an intermittent, for it was supposed to be an effort of the body to relieve itself from some latent seeds of mischief, which would show themselves if the intermittent were cured." (William Heberden. 'Commentaries,' 1806).

In the exploration of America many new remedies were discovered. As early as 1508 guaiac wood or *lignum-vitæ* was made known to the Spaniards by the Indians of Hispaniola, and the interest excited by its application to the newly discovered disease, syphilis, followed some years later by the use of the bark called sarsaparilla for the same disease, aroused the thought of specific cure, a process we now identify with treatment directed to a living known cause, and in both syphilis and malaria with a sterilizing, or at least inhibiting, effect. But not until more than a century after the discovery of America did white people become acquainted with the drug we now celebrate, the indispensable Peruvian bark, fever bark, or cinchona bark, from which we obtain quinine and other alkaloids. If we seek for reasons for the lateness of the introduction, we may find them in the state of civilization at the time.

The seventeenth century was a period of extraordinary intellectual fecundity in Europe. In art and literature it is enough to recall the names of Shakespeare, Bacon, Moliere, Cervantes, and Velasquez. In physics, chemistry, and physiology the fermentation was just as marked though not so easily perceived. Descartes' 'De Homine,' the first book on physiology, appeared in 1622 when bark was barely known, and his epoch-making work on analytic geometry was published in 1637, just before the Countess of Chinchon was given her treatment. Harvey disclosed the first lines of the circulation of the blood nine years earlier, and Malpighi's discovery of the lung circulation was published in 1661,

while the medical use of the bark was still in the cradle. All this time Europe, including the British Islands, was torn by civil and national wars, while the seas were ravaged by rival navies, pirates and buccaneers. In this period a new drug had to suffer comparison with such well-known and time-tried remedies as viper's broth, crab's eyes, and murderer's skulls. Credulity, jealousy, and force of habit hampered the rational discussion of measures for the improvement of medicine.

If the state of Europe was unfavorable for medical progress, that of Peru, where cinchona was indigenous, was even less so. The empire of the Incas, when the Conquerors first cast their eyes upon it, extended about thirty-five degrees of latitude southward from the equator, or from north of Quito to far south in Chili. Huayna Capac, well named the Great Inca, died in 1526, the year before Pizarro landed. Civil war began about the same time, and was intensified after the invasion. The Inca was murdered in 1533, and the Conquest was not completed until 1555. The destruction of a remarkable civilization was no less complete than the alienation of the friendship of the natives. Implacable hatred, fear, distrust, and secretiveness became intensified, and not until near the end of the next century did the Indians abandon their efforts to throw off the Spanish yoke. Under the circumstances it is not strange that we know little positive about early Indian acquaintance with the bark and its entry into medicine. It is, of course, still possible that future explorations in some burial place, or convent, may reveal new and important evidence. As it was, a century elapsed between the first formal use of cinchona bark and the study of its history. The subject has been reviewed many times, with most success, perhaps, by Dr. Conrad Wesselhoeft in 1916 (*New Orleans Med. and Surg. Jour.*). I have repeated the study, for the most part in the original sources, and will give only a brief summary of the results.

In 1737 the celebrated engineer and mathematician, Charles Marie de la Condamine (1701-1774), the botanist Joseph de Jussieu, and others were sent to Peru on a scientific mission, and La Condamine, besides giving a careful description of the cinchona trees, for which he proposed the name *quinquina*, investi-

gated the early records and legends. The first written or printed accounts were all composed many years after the events described. In his report to the Royal Academy of Sciences of Paris (1738) he quoted a Genoese physician, Sebastian Badus ('Anastasis Corticis Peruviani.' Genoa, 1663), and Antonius Bollus, a Genoese merchant trading in Peru, the earliest reporters as to knowledge of the bark by the natives before the Conquest, and agreed with them that the Indians used the bark in fevers by pounding it, steeping it in water for a day, and giving the liquid to the patient. La Condamine cited the prejudice of the Indians toward the Spaniards at the time of his visit. He also quoted a legend for the truth of which he would not vouch. According to this, the native lions were subject to a sort of intermittent fever and had been seen eating the cinchona bark, which suggested the medicinal effect to the aborigines. He concluded that the Indians, at least those living in a district called Malacotas, about two hundred miles south of Quito, were acquainted with the properties of cinchona bark long before the Conquest, but out of hatred for the Spaniards kept their knowledge secret. And still it may be true, as Jussieu stated, that a certain Jesuit was cured of intermittent fever by bark given to him by an Indian chief as early as 1600; and it may be supposed that other Jesuits, especially medical men who accompanied those early missionaries, had similar experiences, not recorded.

Alexander von Humboldt visited Peru much later and devoted a great deal of time and thought to the subject. He denied Indian knowledge of the bark, and as for the lion asserted that the native lions or pumas did not frequent the cinchona forests, or live at their elevation. He concluded that Jesuits accidentally discovered the bitterness of the bark, and on trying an infusion in tertian fever proved its curative effect. Like some later travelers, he found that the natives had an inveterate prejudice against various kinds of cinchona bark, and even in the region where the trees grew, treated fevers by drinking certain aromatic infusions or lemon or lime juice. This was true of Loxa, a center of the bark industry, but at Malacotas, the bark peelers in time claimed to have confidence in bark as a remedy.

Eduard Poeppig ('Reise in Chile, Peru, etc.,' 1827-1832), who

visited the cinchona country a century ago, noted the repugnance of the Indians to the use of bark, and Richard Spruce (Jour. Proc. Linn. Soc. Vol. IV) asserted the same for the natives of Colombia and Ecuador, and stated that in Guayaquil the bark, when given for fever, had to be called by some other name. On the contrary, Johann Jacob Tschudi, travelling in Peru in 1847, said that the inhabitants drank an infusion of green bark for intermittent fever.

Mr. Clements R. Markham, afterwards Sir Clements Markham, who investigated the subject while working out plans for raising cinchona trees in India, found no cinchona bark in the medicine bags of the itinerant healers of the country, and did not find it mentioned by the Inca Garcilasso de la Vega nor by Acosta in their lists of Indian remedies. Henry S. Wellcome, who visited the cinchona forests in 1879 and who believed the aborigines knew about bark, said that graves do not contain cinchona, as they do coca leaves.

The aboriginal name for the bark, "quina-quina," or "kina-kina," is suggestive of early belief in its virtues. "Kina" in the Quichua language means a cloak or covering. Repetition forms a superlative, "bark of barks," and almost always implies medicinal qualities. There is no relation between this kina, sometimes spelled "china" and the China root, radix China, Smilax china, concerning which Vesalius wrote a treatise ('Epistola, rationem modumque propinandi radicis Chynae decocti, etc.,' Basel, 1546), showing the same care and criticism that he gave to anatomy, but the fact that the 'Index Catalogue of the Surgeon General's Library,' third series, gives the reference to Vesalius' letter under Cinchona may lead to confusion. La Condamine tells us that in some parts of Peru the Indians used the word "kina-kina" for a balsam used for smoking. Kina-kina appears to have been long abandoned in native language and other words used instead for cinchona bark. To conclude this part of the subject, it is easy to understand that hatred and suspicion of the invading race might have led to long-continued concealing of the valuable remedy, and equally probable that the so-called superior race might have wished to retain for itself credit for the discovery.

The earliest credible record is to the effect that in 1630 Don Juan Lopez de Cannizares, the Corregidor (governor, magistrate)

of Loxa, then a flourishing city, was cured of intermittent fever by drinking an infusion of bark. This seems to have made no impression at the time. According to Badus, Dr. Joseph Villerobel wrote that some bark was sent to Spain in 1632, a certain ecclesiastic of Alcala de Henares being the first person to whom it was administered, and with success, in 1639. And here, too, it is difficult to understand how so many years elapsed without further interest in the bark.

The next landmark, and greatest one, was formed by the use of cinchona in the case of the Vice-queen of Peru. Senora Ana de Osorio was the second wife of the Viceroy Don Luis Geronimo Fernandez de Cabrera, Bobadilla and Mendoza, fourth Count of Chinchon, whose castle of the same name was near Madrid. When she became ill with a stubborn intermittent fever, in 1638, the Corregidor of Loxa, Don Francisco Lopez de Cannizares, sent some bark to the Viceroy with a recommendation for its use. The Viceroy had it tested on other patients with good results, and the Countess' physician, Don Juan de Vega, gave it to her and obtained a cure. The Countess had a quantity of bark sent to her and gave it to the sick in Lima, whence the name Countess' powder. Leaving Peru in 1639 to return to Spain, the Countess died at Cartagena, Colombia, but the supply of bark she had taken with her reached Chinchon, where it was used, but apparently rather slowly. Dr. de Vega also went to Spain with bark which he sold for one hundred reals a pound, the price seeming to indicate a recognition of the value of the drug. At about the same time the Procurator of the Order of Jesuits of Peru sent a quantity of cinchona powder to the apothecary shop of the Order, in the Palace of Cardinal de Lugo, in Rome, the drug thereby acquiring new names, Jesuit's powder, Cardinal's powder, and Lugo's powder.

Badus seems to have suggested the name cinchona, which was confirmed by the Council of Ghent. Long afterward, in 1742, Linnaeus, in the second edition of his '*Genera plantarum*,' gave the name of Cinchona to the genus. He was ignorant of the correct spelling and died before Ruiz and Pavon, Spanish botanists, who landed in Peru in the year of his death (1778), pointed out the correct way, which is used, I find, in a '*Sammlung verschiedener die Fieber-*

rinde betreffende Abhandlungen und Nachrichten,' printed in Frankfort and Leipsic in 1769. By the time Markham made his eloquent plea for the proper spelling of the genus Linnaeus' name was too well established to be changed. A note on the spelling (called to my attention by an item in the 'Bibliotheca Osleriana'), which appeared in the London 'Lancet' August 12, 1916 (p. 309) signed only by the initial "W," points out that the correct spelling would offer difficulty in Italian as the "CH" would take the sound of "K," instead of that in "cherry" as it would in both English and Spanish. "Cinchona" in Italian would be given the proper sound.

The use of cinchona developed slowly. What was needed, as in all therapeutic innovations, was a large-scale experiment, and what benevolence could not accomplish was probably brought about by the commercial spirit. It is said that the Church at one time refused to sanction the use of the drug because it was the invention of unenlightened savages, but at the intercession of Cardinal de Lugo, Pope Innocent X ordered the nature and effects of cinchona to be examined, and the Pope's first physician reported it to be innocent and salutary. The bark was distributed by the Jesuits to the most distant stations of the Order. Roland Sturm of Louvain (1659) said the Jesuits sold the bark to the rich at high prices, but gave it to the poor. A plan of treatment was devised entitled the 'Schedula Romana,' according to which the drug was to be given in doses of two drachms, in bolus, or in infusion of water or wine, before or at the beginning of the paroxysm. If the bark was of what is now considered normal quality, this would give about six grains of alkaloid at a dose, a fair amount.

In 1652 much interest was excited by the cinchona treatment of the Archduke Leopold of Austria, Governor of the Low Countries, who had a double quartan fever. The attack was checked for a month, then there was a relapse with treatment and recovery, and a third attack in which treatment was refused and death followed. A lively controversy followed. The Archduke's physician, J. J. Chiffletius, published a report ('Pulvis febrifug. orbis American.,' etc. Rome. 1653), in which he asserted that arguments, authorities, and experiences were all against the use of bark. He

said that the bark palliated the fever but fixed the humors, an expression unintelligible now, but of great significance at the time. Cardinal de Lugo caused a reply to be published, under the name Antonius Conygius, asserting that thousands had been cured at Rome by the powder. This was followed by a denunciation by Volpiscus Fortunatus Plempius, over the pseudonym Mellippus Protimus, who predicted the abandonment of the bark. Scarcity and high cost checked the treatment at times, and brought out substitutes. Spurious barks were soaked with aloes to give a bitter taste, and there was no way of being sure of the quality or dose of the drug at hand.

On the Continent discussion and argument gave no promise of enlightenment, but just at this time what was known as the Epidemic Genius of disease, and the practical spirit of English medicine came to the rescue. In the middle of the seventeenth century both malaria and cinchona bark excited much interest in England. So numerous were severe cases of intermittent fever that the whole island was compared to a hospital. Entire families were sometimes carried off by malignant tertians. Many members of the ruling family and the nobility are noted in biographies and letters as ill with ague, sometimes as dying with or without the bark. This appears to have been the case with Cromwell. The leading English physicians of the time all mention the treatment with cinchona, sometimes with characteristic practical vision. So the celebrated Thomas Willis said that the bark checked the paroxysms of fever but did not subdue the disease, and we now know the explanation. Richard Morton threw a light on the medical mores of the time by saying that physicians and apothecaries tried to prevent the use of the bark because its application was so simple that every patient would be his own doctor. Anti-Romish feeling was strong, and many objected to the bark on account of its association with the Order of Jesus. The vitriolic Gideon Harvey said that "people were Jesuited to early graves."

It must be remembered that there were no Institutes nor Academies where medical problems could be studied; the statistical method was unknown; even the simple rules of observation laid down by Bacon were rarely followed. Finally, toward the

end of the seventeenth century, an advance was made by the man recognized then and now as the greatest English physician. Thomas Sydenham was born in 1624 and lived until 1689. Drawn early in the Civil War into the Parliamentary cause and army, he became a captain and missed most of his University work. His friendship with the philosopher John Locke influenced the characters of both men. Sydenham has been well described as a follower of the Baconian method, with the synthetic power of genius. This is no place to speak in detail of his career, but it should be said that by careful study of cases he greatly advanced the knowledge of fevers; first described scarlet fever; and added much to the knowledge of gout, from which he himself suffered. His laconic statement that gout affects more rich men than poor, more wise men than fools, has cheered up many a patient. He studied intermittent fevers with characteristic painstaking and first published his ideas on the use of Peruvian bark in agues in 1666. At that time he was not certain of the best method of administration, nor of the results to be obtained, and even thought it dangerous to check the fever which was looked on as a defensive fermentation.

By 1676 he had accumulated an experience that enabled him to speak with authority all the more impressive from his concise and austere mode of expression. Peruvian bark had become his sheet anchor. He had neither seen nor suspected any evil effects and was sure of the harmlessness of the treatment. The symptoms formerly attributed to the bark he correctly ascribed to the disease. In this he agrees with the enormous experience and accurate observations since the discovery of the germs, and especially in tropical countries. Before him agues were called "*opprobria medicorum*," the reproach of physicians. He had learned that the relapse, which from the first days of bark administration had so puzzled physicians, was due to the blood's not being sufficiently saturated with the febrifuge, and that to avoid it the treatment must be repeated. This matter has also received extensive study and confirmation in the last decades. He gave an ounce of bark in twelve doses, one every four hours, corresponding to about twenty-five or thirty grains of alkaloid, a proper dose at the present time. Following his Baconian instincts he

avoided speculation on the mode of action of the remedy, saying he would as soon account for the greenness of grass. For the relapses he insisted on repeating the treatment every fortnight, which is efficient in most cases but in others has to be modified by shortening the period to five days. Finally, he objected to vehicles, such as wine and syrups, to carry the medicine into the stomach, and attributed their use to ignorance and fraud.

The last statement may well have been directed against one who, in the minds of many, even some medical men, deserved more credit than Sydenham for the introduction of bark in the treatment of agues. The other was one Robert Talbor, a "scholar" of Cambridge when Sydenham began to practice. Settling in the malarious fen district of Essex, he became familiar with the use of cinchona bark and later practised successfully in London, where he had various people of fashion as patients and was fortunate in curing Charles II, who ordered the College of Physicians not to interfere with Talbor's practice. He was made Physician to the King, later knighted at Whitehall with a patent of August 7, 1678, and an annuity of one hundred pounds. In 1679 he visited Spain and Paris, treating many notable people. Aided by the celebrated Madame de Sévigné and her friends ('Robert Talbor, Madame de Sévigné, and the Introduction of Cinchona,' by George Dock, M.D., *Annals of Medical History*. Vol. IV. No. 3, 1922), in the face of opposition by the medical profession, he was allowed to treat the Dauphin for intermittent fever and after curing him, the King, Louis XIV, bought the secret of the preparation used by Talbor for a large sum and had it published as "The English Remedy." Soon after that Talbor's picturesque career was ended by his death.

There is no reason to believe that Sydenham owed any of his knowledge to Talbor, as was argued at the time and afterwards. In the words of Dr. R. G. Latham, who edited one of the best translations of Sydenham's works: "Whether Talbor or Sydenham was the most sagacious physician is an open question. Which of the two possessed most of that liberality that becomes his profession is a settled one. What Sydenham gave away, Talbor sold." The combination of careful investigation and candid, restrained reporting by Sydenham, and the spectacular adver-

tising genius of Talbor seem to have fixed the value of cinchona bark for two hundred years, or until the more exact methods possible after discovery of the blood parasites opened a new epoch. In those two centuries nothing essential was added, and even in the last fifty years we have merely confirmed what was previously known. Before Laveran, we had what was known as the therapeutic test. If a fever yielded to quinine, which was isolated in 1820, it was considered malarial; if not, further study was necessary. Unfortunately, many physicians did not know how to use quinine or how to evaluate the results of treatment.

The discovery of the parasites permitted an exact diagnosis in most cases with great accuracy and promptness. Details of dosage and administration are still subjects for discussion as they were from the beginning, but as my friend C. C. Bass, one of the most sagacious students of malaria, has recently said (*Jour. Amer. Med. Assoc.* Oct. 4, 1930, p. 988): "There are almost as many methods of treating malaria with quinine as there are authorities on the subject." This certainty of cutting short the attacks is the remarkable thing about quinine, giving it the right to be spoken of as a specific. It is not my part to discuss how the effect is brought about, but there is a practical point on which a few words may be said. Malaria, like most diseases, has a strong tendency to recovery in each attack, with a tendency almost as strong to relapse. It might seem proper to let the patient take a chance at natural cure, as we do in many other diseases, with due regard to the patient's welfare and comfort. But the danger in malaria is definite and peculiar. Each paroxysm coincides with the destruction of red blood corpuscles, which even in a mild case may be quite extensive, and in a severe one may amount to a loss of one-fifth or more of all the blood corpuscles in the body within forty-eight hours. This equals a direct loss of more than a quart of blood. As we can cut the attacks short with almost absolute certainty and very little risk, the reason for exact treatment based on accurate diagnosis is clear.

Malaria is one of the diseases in which individual preventive treatment should always be applied. The details may vary considerably but the principle is to give the patient a sufficient dose of quinine at short intervals to check the development of the

parasites, trying to avoid making the parasites what is called "quinine fast," that is, resistant to the poisonous effect. As a matter of fact this is not a frequent occurrence. Preventive treatment can also be used in people who have not had malaria but who are obliged to go into a malarial district. Regular doses of quinine, combined with measures to lessen the risk of mosquito bites, will do much to prevent an infection.

From an early period cinchona bark and later quinine and other cinchona alkaloids were tried in every conceivable disease, but in no other than malaria are such striking effects observed. If a reduction of high temperature is desired quinine may be used. As a tonic, that is, for improving appetite and energy, it is of distinct value. It may be used with advantage in influenza, whooping cough, and some other acute infectious diseases. It is of value as a local anesthetic, and has a distinct usefulness in many important cases of heart disease. Further details would be irrelevant. On the whole a seventeenth century writer was perhaps not far from the truth when he said that cinchona bark was more precious to mankind than all the gold and silver the Spaniards brought with them from South America.



DR. SAPPINGTON

From the original oil portrait by Bingham in the Old Tavern, Arrow Rock, Missouri.

DR. JOHN SAPPINGTON, PIONEER IN THE USE OF QUININE IN THE MISSISSIPPI VALLEY

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In the second wave of migration to the Middle West, that which followed the War of 1812, a physician came to the Territory of Missouri who, in the practice of his profession, exerted extraordinary influence toward making habitable the Mississippi Valley. The significance of his achievement is not appreciated and his work is almost forgotten. This brief paper aims to record the quinine treatment of malaria as a factor of first importance in establishing homes and industry in the great Valley, and to pay tribute to the memory of Dr. John Sappington, by whose wisdom, knowledge, energy, and patience, quinine was introduced and distributed throughout the newly acquired Louisiana Territory.

The immigrants to the Mississippi Valley encountered the usual hardships connected with the settling of an American wilderness; but in addition to the ordinary, if severe, trials of courage and endurance, there was ever present in the Valley the menace of the dreaded intermittent fevers against which means of protection were unknown, and for which the drastic treatment of the times was ineffectual. Very few immigrants escaped. The death rate in Sappington's time, it is stated, reached twenty-one in every one thousand of the population of Missouri. Destroying the blood, malarial fevers left the survivor anaemic, weak, spiritless, and incapacitated for work of any kind for longer or shorter periods. Once the parasites were lodged in the system, in the absence of the remedy, they tended to remain, and attack followed attack. Work was brought to a close, hope of recovery was abandoned, plans of settling were changed, the victims sought other, more healthful regions, or returned to the homes from whence they had come. Enterprise and progress in the older settlements on the Mississippi were being stifled by endemic in-

¹ The author takes this opportunity to acknowledge gratefully the aid generously given in the preparation of this address by the Missouri Historical Society, St. Louis, and by the Old Tavern, Arrow Rock, Mo.

termittent fevers. Knowledge of the menace of malaria deterred many from emigrating from eastern states to the Valley, notwithstanding the promise of rich soil, low cost of farm land, and conditions favorable for trading.

Historical treatises have laid the emphasis upon the succession of political events of a state and treat briefly or ignore certain other powerful factors that operate to determine the kind and quality of a community and its rate of progress in civilization. Among the neglected factors in the history of the Mississippi Valley must be reckoned the widespread presence of an endemic disease, sometimes fatal and always deleterious in its severe and prolonged effects upon the constitution. The cogency of this assertion will appear to any one who will examine the original sources of information concerning disease in the Middle West during the period of American settlement, to be found in the medical treatises of that time, in the official reports of explorers and in the accounts given by immigrants and travellers in that region.

THE MALARIA MENACE TO SETTLING THE MISSISSIPPI VALLEY

As it is my plan, first, to try to depict the malaria menace which immigrants encountered, and, second, to present the work of Sappington, evidence of the disease will now be adduced from the literature on the Valley in the period 1802-1850. Some of the most important papers which throw light on this subject are in the original very rare, but may be found carefully reprinted in Thwaites'¹ admirable collection to which frequent references will be made. Intermittent fevers are noted in the accounts, and the conditions of the sufferers and the effect upon settlements are often described in detail. The quotations which follow have been selected to prove the wide distribution of malaria encountered by immigrants, its devitalizing consequences to the victims and its influence in inhibiting the progress of home making and industry in the valley.

Cuming, writing (1808) of Palmyra in the Mississippi Territory,² says:

¹ Thwaites, R. G. *Early western travels, 1748-1846. I-XXXII*, Cleveland, 1907.

² Thwaites, *op. cit.* IV, Cuming F., *Tour of the West.*, p. 307.



DR. SAPPINGTON'S RESIDENCE NEAR ARROW ROCK, MISSOURI, AS IT
APPEARED IN OCTOBER, 1930.

I think the lake and swamp behind Palmyra must render it unhealthy, and the pale sallow countenances of the settlers, with their confession that they are annually subject to fevers and agues, when the river begins to subside, confirms me in my opinion. Indeed this remark may be applied to the banks of the Mississippi in the whole of its long course, between the conflux of the Ohio and the Gulph of Mexico.

Regarding Natchez, the same author states:

. . . the high cliff or bluff which overhangs the river, . . . contributes to defend the town from the noxious vapours generated in the swamps immediately on the river banks, yet not so effectually as to prevent its being sometimes subject to fevers and agues, especially from July to October inclusive, when few strangers escape a seasoning, as it is called, which frequently proves mortal. The surrounding country at a little distance from the Mississippi, is as healthy as most other countries in the same parallel of latitude. The landing, where are a few houses immediately under the bluff, is particularly fatal to the crews of the Ohio and Kentucky boats, who happen to be delayed there during the sickly season.

Of Bayau Pierre, Cuming wrote:

On the subsiding of the waters, the sickly season commences, and lasts with little variation from July to October, inclusive. . . . The prevailing malady is a fever of the intermittent species, sometimes accompanied by ague, and sometimes not. It is rarely fatal in itself, but its consequences are dreadful, as it frequently lasts five or six months in defiance of medicine, and leaves the patient in so relaxed and debilitated a state that he never after regains the strength he had lost. It also frequently terminates in jaundice or dropsy, which sometimes proves fatal.

From Estwick Evans³ comes the following observation: "The climate, judging from the general appearance of the inhabitants, I should suppose much less healthy than that of New-England; and in particular situations the fever and ague, and bilious fevers are very prevalent."

Flint⁴ has given his impression of the prevalence of bilious fever and endemical disease in Kentucky and Illinois at the confluence of the Ohio and Mississippi Rivers:

The inhabitants in the neighborhood of the Falls have been visited by attacks of bilious fever and ague. A considerable number of persons have been carried off by the former of these complaints, and the convalescent of both are much debilitated. . . . Accounts from Vincennes say, that about a third part of the people there are confined to bed by sickness, and that much of the Wabash country, both in Indiana and Illinois, are now subject to the same evil. Reports from the settlements on the lower parts of White River represent that sickness pre-

³ Thwaites, *op. cit.* VIII, Estwick Evans, *Pedestrian tour.*, p. 256.

⁴ Thwaites, *op. cit.*, IX, James Flint, *Letters from America*, pp. 287, 164.

vails there and along other water courses. . . . The endemical distempers of this country, so far from being chiefly confined to the weak and the aged, seem to commit their greatest devastations amongst the young and the strong. Surviving sufferers are frequently rendered unfit for labour for a third or fourth part of the year, and receive an irreparable injury to their constitutions; regimen and medicine become almost as indispensable as food; productive labour is thus diminished, and an additional cost imposed on life.

Routes of travel through the fever country were avoided as Flint points out:

At present, a passage from New Orleans to the falls of the Ohio costs 100 dollars, including provisions. Goods are carried at 6¼ cents per pound weight. This high rate, with the danger of passing through a most unhealthy climate, in case of arriving after the beginning of July, or before the end of October, gives Baltimore, Philadelphia, or New York, a decided preference to Europeans who would settle in the lower parts of the Ohio country, or on the Missouri.

Concerning the French settlements, Flint⁵ wrote: "The inhabitants seem indolent, yawning as if under the constant influence of fever and ague; which, in fact, they often have."

Discouragement to immigrants, caused by attacks of malaria, is expressed again and again in the early narratives. The following is taken from Welby:⁶

A large party of settlers from the state of Illinois came by, they are returning to that of New York, to the same spot they quitted a year and a half ago. The account they give is that a fine fertile tract of land about forty miles from the river Illinois, and not far from its confluence with the Mississippi, was purchased by them, and they settled upon it last summer; since which period they had lost eight of their party by dysentery, fever and ague, and that the remainder had determined to quit the purchase, and return with the loss of all their time and nearly all their money.

The early settlers were often compelled to move, after having cleared a farm, on account of the unhealthfulness of the spot. Nuttall⁷ mentions one of these incidences occurring in Ohio: ". . . they had settled on a piece of alluvial land, and might probably have prospered, but for the dreadful effects of continued sickness (ague and bilious fever), which urged them to sacrifice every other interest for that of their emaciated offspring and to ascend the Ohio in search of a situation which might afford them health."

⁵ Recollections, p. 97, quoted by Carl O. Sauer, *Geography of the Ozark Highland*. Geog. Soc. of Chicago, Bull. 7. 1920.

⁶ Thwaites, *op. cit.*, XII, Adlard Welby, *A Visit to North America*, p. 211.

⁷ Thwaites, *op. cit.*, XIII, Thomas Nuttall, *F. L. S.—A journal of travels into the Arkansa Territory*, p. 50.

In James' account of Long's Expedition⁸ we find the following references to fever and ague in Pope County, Ill.: "In a few miles we arrived at another cabin, where we found every member of the numerous family sick with ague and fever, except one young girl."

"On arriving at Golconda, Dr. James had become so much indisposed, by a recurrence of fever and ague, as to be unable to proceed."

Ogden⁹ wrote: ". . . fevers and agues prevail more or less during the summer season; yet the country and climate are allowed, by the best judges to be the healthiest in the world."

Writing about Natchez in 1827, Bullock¹⁰ observes: "It has been tried as a summer residence by some of the inhabitants of New Orleans, but the scourges of this part of America (fever and ague) extend their ravages for more than 1000 miles higher up."

Flagg¹¹ has left several graphic descriptions of the endemic fever and ague menace in the years 1836, 1837. In ascending the Illinois River, he wrote:

It is not surprising that all these regions should be subject to the visitations of disease, when we look upon the miserable cabin of the woodcutter, reared upon the very verge of the water, surrounded on every side by swamps, and enveloped in their damp dews and the poisonous exhalations rising from the seething decomposition of the monstrous vegetation around. The traveller wonders not at the sallow complexion, the withered features, and the fleshless, ague-racked limbs, which as he passes, peep forth upon him from the luxuriant foliage of this region of sepulchres; his only astonishment is, that in such an atmosphere the human constitution can maintain vitality at all.

Writing from Monroe County, Ill., he says:¹²

But, of all other epidemics, the "fever and ague" is the scourge of the West. Not that it often terminates fatally, except by superinducing a species of consumption; but, when severe and protracted, it completely shatters the constitution; and, like Mezentius, the victim ever after bears about him a living death. In its lighter form, most of the settlers at some time or other experience it, as it is brought on by exposure:

⁸ Thwaites, *op. cit.* XVII, Maj. S. H. Long, Account of an expedition from Pittsburgh to the Rocky Mountains, pp. 33 and 92.

⁹ Thwaites, *op. cit.* XIX, George W. Ogden, Letters from the West, p. 77.

¹⁰ Thwaites, *op. cit.* XIX, W. Bullock, Sketch of a journey through the Western States of North America, p. 131.

¹¹ Thwaites, *op. cit.* XXVI, Edmund Flagg, The Far West, p. 127.

¹² Thwaites, *op. cit.*, XXVII, p. 96.

And again, in the neighborhood of Cahokia, Flagg¹³ wrote: "The poisonous night-dews caused by these marshes, and the miasm of their decomposing and putrefying vegetation, occasion, with the sultriness of the climate, bilious intermittents, and the far-famed, far-dreaded '*fever and ague*,' not unfrequently terminating in consumption. This circumstance, indeed, presents the grand obstacle to the settlement of the American Bottom."

We find in Michaux's¹⁴ narrative respecting Alexandria in Mississippi Territory and West Tennessee: "The population would be much more considerable, if the inhabitants were not subject, every autumn, to intermittent fevers, which seldom abate till the approach of winter."

"West Tennessee is not so salubrious as Holston and Kentucky. A warmer and damper climate is the cause of intermittent fevers being more common there."

Quoting Featherstonhaugh and Stoddard, Sauer¹⁵ points out the dangers to settlers locating in the bottoms of the Mississippi.

"Their sallow, emaciated countenances, that looked distressed by the monstrous quantities of calomel they were accustomed to take, and the feeble and uncertain steps with which they went about their avocations, betrayed how dearly they paid by the loss of health for the privilege they enjoyed of occupying a fertile soil." As a result of the prevalence of fevers few Americans were willing at first to locate in the Mississippi lowlands, preferring generally the uplands. The lower valleys of the St. Francois, Castor, and Black Rivers were also very unhealthy, as they were drained poorly. In Greenville, on the St. Francois, the first settlers were said to be dying "by inches of chills and fevers."

The effect of malaria on the location of towns is apparent from the observations of James (1819) quoted by Sauer.¹⁶

"Numerous other towns . . . containing from one to half a dozen houses each, are to be met within a few miles. . . . Almost every settler, who has established himself on the Missouri, is confidently expecting that his farm is in a few years to become the seat of wealth and business, and the mart for an extensive district." Almost without exception these places were located on the river flood plain at landings. Consequently they were malarial, subject to flooding, and in time most of them were destroyed by the river. The fate of Franklin was foretold within seven years of its foundation. Of the entire number only two remain, Boonville and Jefferson City, both located on the river bluffs.

¹³ Thwaites, *op. cit.*, XXVII, p. 107.

¹⁴ Thwaites, *op. cit.*, III, F. A. Michaux, *Travels to the west of the Alleghany Mountains*, pp. 186, 276.

¹⁵ Sauer, *op. cit.*, p. 114.

¹⁶ Sauer, *op. cit.*, p. 112.

The chief source of information in medical literature relative to disease in the Mississippi Basin in the first half of the last century is the monumental work of Daniel Drake, the distinguished physician, investigator and scholar. The two large volumes of 'A Systematic Treatise on the Principal Diseases of the Interior Valley of North America,' 1850, 1854, are the outcome of "long journeys of observation, repeated through a large part of several years" and extensive correspondence with physicians practising in the Valley.

Part I of Book Second, 162 pages, is devoted to the consideration of autumnal fever in its various modifications. The concluding words bear testimony of the prevalence and serious nature of this disease: "The article Autumnal Fever is now brought to a close. It has extended through many pages; but a smaller number would not have sufficed, to present, even an outline, of its etiological, and therapeutic history; through so wide a geographical range, as that of the southern half of our Interior Valley; in almost every part of which, it is an annual endemio-epidemic. Of all diseases, it is the one which has the most intimate relations with soil and climate—that, in which, peculiarities, resulting from topographical and atmospheric influences, are most likely to appear . . . It is, moreover, the *great* cause of mortality or infirmity of constitution, especially in the southern portions of the Valley; and therefore entitled to severe and patient attention."

It is evident by the accounts given that there was no discrimination of victims seized by the fevers; all who entered the lowlands were liable to attacks. Several of the authors of the narratives quoted were stricken. John Bradbury, the English traveller, suffered from intermittent fever while stopping at Manchester near St. Louis. Nuttall mentions his attack while at Grand River and of a recurrence of the disease. Nearly every member of Long's party was sick and incapacitated by malaria while at Cape Girardeau, October, 1820. Buttrick was the victim of several attacks as mentioned in his 'Voyages.'

Whereas a few of the early writers on the Mississippi Valley do not refer to malaria, or appear not to recognize it as an obstacle to settlement, they are the exceptions among the majority

who have described the presence and dire effects of this malady. Any one now reading the original accounts of the many men living in or travelling through the Valley cannot fail to draw the conclusion that the widespread endemic intermittent fever was a factor exerting great influence upon the progress of settling and upon the constitution of the early settlers.¹⁷

Quoting Sauer (p. 115), who refers to Brackenridge and Baudis-sin, "The control of malaria has been a slow and difficult matter. In 1811 it was observed that the disease was due partly to decaying vegetation. It was discovered early that the clearing of the land reduced the fevers. Chiefly by thus reducing the breeding places of the mosquito through clearing and drainage, the larger river bottoms have been made tolerable." It was not, however, until the introduction of quinine that the disease came under control, that restoration to health could be expected, permitting work to be resumed and to be continued with a hopeful outlook and confidence in the future development of the land and settlements.

THE INTRODUCTION OF QUININE

Events in the life of Dr. John Sappington of Arrow Rock, Saline County, Missouri, have been recorded in several biographies.¹⁸ The great influence of his contribution, bringing into use the quinine treatment of malaria in the states of the Mississippi basin, seems, with one exception, to have been passed over by his biographers. That exception is Dr. Thomas B. Hall, who fully appreciates the significance of Sappington's work.

¹⁷ Whether malaria existed in the Western Hemisphere prior to the discovery by Columbus is not known. The physical condition of the Indians may be taken as evidence against its presence. There can hardly be any question as to the spreading of the disease by the importation of negroes carrying myriads of the plasmodium to the New World. In North America the southern states were early subjected to endemic intermittent fevers. Towns along the Mississippi, to which negroes came with the Spanish settlers, were paralyzed in their growth by the fevers.

¹⁸ Drumm, Stella M., ed. *Down the Santa Fé Trail and into Mexico. Diary of Susan Shelby Magoffin, 1846-1847.* Yale Univ. Press. 1926; Hall, Thomas B., *John Sappington.* Missouri Hist. Rev., XXIV, 1930; Napton, William Barclay, *Past and present of Saline County, Missouri.* Indianapolis, 1910; Rainey, F. C. *Along the Old Trail.* Marshall, Mo., 1914; Stevens, Walter B. *Centennial History of Missouri,* article by Dr. Frank Lutz, II, p. 75. St. Louis, 1921.

Further research into Sappington's career must yield additional matters of interest, for he was a man of unusual originality; but for the purposes of this paper sufficient material is at hand to make, I trust, a convincing story of the part he had in the control of malaria over a large part of the United States.

Sappington came with his wife to Howard County, Missouri, in 1817 and later moved to Arrow Rock in Saline County, where he established his home, called Fox Castle. He had practised medicine for about ten years at Nashville, Tennessee, with his father and independently, and it is to be noted that he had an extensive experience in the treatment of malaria. In 1814 and 1815 he attended lectures in medicine in Philadelphia. According to Hall¹⁹ Sappington had a diploma from the University of Pennsylvania. In 1844, when Sappington was in his sixty-eighth year, he wrote and published a book²⁰ on fevers, setting forth therein his methods of treatment and the conclusions he had reached from a long period of practice dealing with various fevers. We learn from this little book of Sappington's revolt against the then orthodox treatment by the practice of depletion and of his insistence on the administration of cinchona extracts and quinine, in which drugs he shows absolute confidence in their power to control intermittent fevers. One learns in reading Sappington's book, that the author in attacking the doctrines of Rush and Cullen had no more knowledge to offer and consequently no better theories concerning the cause and treatment of fevers. What seems to have guided him and held him to his belief in the use of quinine was not so much his theories on fever as the actual effect upon temperature and the prompt recovery of the patient which he observed following the administration of the drug. The quotations from Sappington's book which follow will show, I hope, the author's great work in compelling the general recognition of the use of quinine in the Mississippi Valley, and something too of his vigorous and independent character.

Sappington says on p. 21 of his book:

¹⁹ Hall, *op. cit.*

²⁰ Dr. John Sappington, *The theory and treatment of fevers, revised and corrected by Ferdinand Stith, M. D., Franklin, Tennessee. Arrow Rock: Published by the author. 1844.*

I commenced the study of medicine about the time that Cullen and Rush, at the head of their respective schools, were lecturing and promulgating to the world their views on blood-letting and other modes of depletion, then adopted by the followers of the depletive or antiphlogistic theories. I was instructed in those doctrines, and after having practised with my preceptor for about five years, who was a scientific and experienced practitioner, and who was inclined to the Brunonian and Darwinian doctrines, using tonics and stimulants earlier and more generally than was common, I entered on the duties of my profession on my own responsibility, and was at least as successful as those around me.

Further, on p. 22, appears:

After having practised medicine several years, and having undergone a considerable change in my views and opinions relative to the nature and character of some diseases and some remedies, I attended a course of medical lectures in the University at Philadelphia, where I became confirmed in the opinion that I was reasonably acquainted with the different theories and practices of the day, but which only served to confirm me of their error in very many particulars.

The orthodox treatment of fevers against which both in theory and practice Sappington rebelled, is set forth in ironical language on p. 53.

The depletists contend that their treatment is necessary and proper, if not to subdue inflammation, to guard against it; hence they take blood. The febrile heat and hurried action still continuing, they administer pukes, they say to expel morbid matter, and thereby subdue the disease. The heat of the skin and perturbed action still continuing, they administer purgatives, still to reduce the fever and to rid the system of morbid matters. The fever still runs on, they repeat their bleedings, emetics or cathartics, still to reduce or to eliminate morbid matters from the stomach, bowels, or gall-bladder, under the title of vitiated bile. But the fever still hangs on. They now begin to tighten the reins of government, and hold up a little; in the language of their grave consultations, these remedies they say have been pushed as far as the subject can possibly bear. Well, what next? Now comes either a course of nauseating and sweating drugs, or else the alterative doses of blue mass or calomel. By this time the race is nearly run; the patient either begins to mend in spite of the doctors, or retreats from their custody.

Let these passages suffice to mark Sappington's independent spirit and his convictions in respect to the drastic treatment of fevers then the routine practice of his colleagues, and let us pass on to some of the evidence of his knowledge of malaria as shown in his book. On the classification of intermittents the nosologists are subjected incidentally to a little criticism; on p. 93 we find:

The term intermittent, or ague and fever, is applied to that form of fever which is characterized by distinct and perfect intermissions, or periods of exemption from febrile symptoms. Having never yet been able to discover any

utility in that extravagant love of words and of mere verbal displays, which has induced the nosologists to affix a name, a term, or a title, to every symptom, whether trivial or otherwise, that might perchance accompany this form of fever, we shall content ourselves with the introduction of those only that are the most common results of its natural periodicity; such as quotidian, tertian, quartan, and their subdivisions into double, treble: and so forth, and this division even, so far as the treatment is concerned, we consider of no importance, since in whatever form it may appear, its nature is the same, and the proper treatment, with but slight modifications, should ever be the same also.

Regarding the symptoms, a rather complete picture is drawn on p. 94.

The attack usually commences with a sense of lassitude and weakness, with a yawning and stretching; quickly followed by coldness, rigors, and trembling; then comes a paleness and lividity of the extremities; laborious respiration, anxiety, nausea, sometimes vomiting; pulse frequent, small, and feeble, though sometimes more slow; thirst great; the skin generally sensibly corrugated, and of a more or less livid hue, urine pale and scanty. These symptoms constitute the first or cold stage; which often continuing for a longer or shorter time, is succeeded by a heat or redness of the skin, particularly of the face; the respiration becomes fuller, stronger, and more free; anxiety less, pulse fuller and stronger; thirst still great, with more or less pain of head, back, and the limbs. This stage is again succeeded by the third or sweating stage, when a remission of all the symptoms takes place under a more or less abundant perspiration, sometimes attended with an increased discharge of urine and dejections from the bowels.

The intermittent is justly considered the mildest form of fever, and when rightly treated in the commencement or before it has continued many days, is usually the most manageable form of fever that we have to contend with: but when neglected and suffered to run its course for a time, a long list of formidable diseases or results is apt to follow in its train, such as engorgements and enlargements of the spleen, pancreas, and liver; attended with febricula, indigestion, and not unfrequently followed by watery effusions or dropsies of the abdomen and of the whole body.

In treating intermittent, or ague and fever, Sappington is not an advocate of bleeding (Dr. Rush, he says, favors its use), and he finds little need for emetics and cathartics excepting to meet special indications (an overloaded stomach, constipation). "As to the use of cathartics, we are well aware that some of the learned professors of the schools have strongly advocated, and placed great reliance on them, under a belief that the disease was caused by a congestion in the liver, and that the use of drastic cathartics constituted the most efficient means of relieving that viscus: But we hope that we have already succeeded in convincing the reader of the fallacy of such reasoning."

The author's treatment by quinine may now be described:

What, then, do we conceive necessary to be done?—that is the question. Simply to combat the fever by the use of tonics, aided with sudorific drinks, during the hot, or febrile stage, and prevent its recurrence by the continuance of the tonic remedies (quinine) during the intermission. For this purpose we have found one grain of quinine every two hours,—both day and night,—regularly administered through all stages, sufficient for all salutary purposes; and if the dose were augmented to two grains, during the same period of time, we should apprehend no bad consequences therefrom. We have aided its action on the skin, during the hot stage, by the use of warm diaphoretic teas, such as sage, and Virginia snake-root . . . So soon as a general perspiration is excited, or the febrile symptoms are caused to abate, then discontinue the use of the sudorifics, and continue that of the tonics alone.

In a foot-note (p. 97) Sappington states: "As in this form of fever the patient is more liable to relapse than in any other, when once the disease is arrested, he would do well to take two or three doses of quinine a day, until his strength and complexion are restored."

Sappington's interest in quinine seems to have been started by his reading in an old pamphlet of the accidental discovery of the curative properties of Peruvian bark (p. 23). But although having learned by personal experience of its effect upon fevers, Sappington, like others of his time, was for some years prejudiced against it. On p. 80 two reasons for the prejudice on the part of the profession are set forth: "The obstacles, with our predecessors and contemporaries, to the discovery and adoption of what we hold to be truths (that is, the aptitude of quinine to the cure of fever,) are two-fold; namely, a belief in the inflammatory nature of fever, in the first place, and, secondly, of a stimulating or inflammatory property in the nature of quinine." Whereas Sappington's chemical differentiation of quinine from the class of stimulants will not appear now as very convincing, his proposal to prove its effects by observation on the living makes its appeal to the experimentalist of to-day. Sappington writes:

But there is still another way by which to arrive at truth: it is, the testimony of the facts of human experience, or of human observation on human sensibility; alias, the phenomena in living human matter.

Now, when we consult the pages of history, from the period of the first discovery of the virtues of the Peruvian bark, A. D., 1500, we find febrifuge properties ascribed to it. From that period to the present, in the hands of different chemists and different practitioners, have its properties, and its varied re-

medial uses, been differently represented. Still we find that the sum of the testimony—the sum of the experiments and researches, up to this day, have tended rather to advance, than to detract from its virtues; nearly all writers admitting its antiseptic and its tonic properties, while some in a limited sense were willing to ascribe to it febrifuge and alterative virtues. The weight of our own personal experience will go to show, and to give to it, all the virtues for which it has, as yet, obtained credit, and even more. In our hands, for years past, in some form or other, has it succeeded, in a far more eminent degree than any other article of the whole *materia medica*, in contending successfully with fever, of whatever type, and in whatever stage it has come before us.

The following quotations (pp. 84, 85) are of much interest in proving Sappington's knowledge of the prophylactic use of quinine and in giving an insight into the means and extent of distribution of the drug under his direction:

We are not only satisfied as to the curative powers of quinine, but we are disposed to ascribe to it preventive virtues also. To this conclusion are we led not only from experiments made in the author's own family; but from facts occurring in the experience of his travelling agents.

He has had for the last eight or ten years from fifteen to twenty-five agents employed in the distribution of his pills, each travelling from three to six months every year. These agents have been sent to all those states and to such portions of them too, as were considered the most sickly; they were generally sent off early in the spring, and seldom returned earlier than June, July, or August, and not unfrequently set out again in the heat of summer to the most sickly regions of country. These agents were all instructed to use the pills occasionally as a means of protection against the influence of malaria, and there has never yet occurred a single instance in which any one of them has contracted a fever of any kind.

From these facts we are led to infer that if quinine was judiciously used in sickly countries and in sickly seasons, that such a thing as fevers of any type, would rarely if ever occur, excepting under circumstances of the combined operation of the many causes.

When quinine is used as a preventive, an adult should take a dose of one grain three or four times a day, until he takes twenty-five or thirty grains. This quantity should be taken every two, three, or four weeks, until the sickly season is over, or the epidemic has subsided. Children should take less in proportion to their age.

While Sappington himself was convinced of the efficacy of quinine in the treatment of fevers, there is much evidence in his book indicating the struggle he must have had to persuade others to his belief. The medical profession showed little interest or opposed its use, as we are told in the passage quoted above and as appears in many places in his book (Cf. Drake *op. cit.*, II, 98 ff.). Some part of this opposition was based on the misapplication of the drug, so Sappington asserts (footnotes, p. 136).

In the first place, in the earlier periods of its introduction into practice, physicians could not well have attained to a knowledge of its full virtues, by reason of the bulk of the inert cortical mass with which it was encumbered, causing it to disagree with the stomach, they not having learned to extract its salts, the quinine in which its virtues are concentrated . . .

Some have erred in using doses too small or at intervals too long, while others again have run into the opposite extreme. Some again may have been disappointed, from the unfavorable condition of the patients on whom their experiments were made. One thing certainly is passingly strange; that is, that, while all agree in ascribing to the drug febrifuge properties, scarcely any are willing to administer it while there is the slightest fever.

Sappington found that his patients, too, objected to taking quinine (p. 26).

Partly owing to the prejudices of the people, causing them to fear that it would increase their fevers, and partly to the fact that, in some instances, the stomach would not retain it, or that it would pass off on the bowels as a purgative,—in either event my object was more or less defeated.

The names of Pelletier and Caventou who first separated the pure alkaline salt, called quina, from the bulky and inert mass in which nature had placed it, deserve to be remembered with gratitude by all mankind.

Since that fortunate era in medicine, I have been enabled to administer the bark at any stage, and in any quantities that I might think advisable, without fear of injury to my patients, or exciting any fear in their minds. This discovery has not only afforded me heart-felt gratification,—for the reason that it enabled me to give more prompt and certain relief to the sick,—but it has been instrumental in giving to me a character and standing in my profession, well calculated to excite the envy of the physicians around me. But this I desired not; for I did not conceal from them, in our consultations, my views on either the theory or practice which gave me such superior success. It seemed that the most melancholy experience was not sufficient to convince them of their errors, and they still, from the mere force of education, considered my practice as empirical.

Aware of this opposition, believing in his remedy and determined to give the people its benefits, Sappington prepared his famous Anti-Fever Pills, “concealing their composition that they might acquire a reputation upon their own intrinsic worth” (p. 22).

Now that the virtue of these pills to the amount of at least one million of boxes has been tested by the people of the United States, and of the Republic of Texas, and up to this date have maintained an improving reputation; thereby sustaining the correctness of my theory, for the mystery is not more in the drug than in the use I have made of it; I presume that the public will begin to see how strangely and unjustly the medicinal properties of the Peruvian bark and its preparations have been perverted, and that instead of its being injurious when taken in the hot stage of fevers, as has been frequently said of it, it is not only entirely safe and beneficial in that or any other stage, but it is the best febrifuge, tonic and antiseptic known.

On pp. 197–199 are given the preparations of cinchona, dosage, formulae and directions for their use. Families are advised “to procure the quinine at the stores, or apothecaries’, as they do their sugar, coffee or tea; and to prepare it themselves, as recommended in this treatise.”

Some conception of the amount of quinine distributed by Sappington chiefly in the malarial regions of the Mississippi Valley is obtained from the preceding quotation. The following item taken from Sappington documents now in the historical collection of the Old Tavern at Arrow Rock, is in further confirmation of how vast were the quantities of quinine that moved from Philadelphia to fever-stricken people in the West.

“Agreement, Sept. 20, 1842 between John Sappington and Sons of the County of Saline and William Hogan and Thomas C. Wright of the Counties of Pettis and Cooper and all of the State of Missouri—to put into hands for collection notes, receipts and accounts amounting to the sum of twenty three thousand, seventy two dollars and seventy nine cents due to John Sappington for *medicine* in the Republic of Texas.” It was also agreed to deliver to the said parties ten thousand boxes of Sappington’s Anti-Fever Pills at sixty cents per box.

It will be apparent to the reader of that remarkable book ‘The Theory and Treatment of Fevers,’ that the author in resolutely defending his theory and treatment was suffering from the wounds which are inflicted upon those who turn out of the established road to blaze new trails. Besides, he suffered because his early preceptorial training in medicine, although a recognized system at the time, did not give the standing at once that the diploma from a medical school conferred. His antagonism to schoolmen in general may have developed from early clashes of his practical knowledge with the theories of some of his school-trained fellow physicians. These observations are intended in no wise to represent John Sappington in the role of a martyr, but to add emphasis to the fact that he accomplished his great work in the absence of coöperation from members of his profession. Let it be remembered too that there was no governmental project supported by public funds to remove the malarial menace from the Louisiana Territory, although the region was being settled at the cost of the health of the immigrants.

Factors which combined to make the Valley habitable were the clearing and draining of the land, reducing the breeding places of mosquitoes, and the introduction of quinine to control malaria. Sappington could not visualize the future results of his purpose and industry in distributing quinine. He was carried away with the knowledge of the efficacy of the drug in the treatment of fevers and in being able to convince the people and the profession in the Mississippi Valley of its use. He exulted in the contemplation of the overthrow of the depletion theory, the first conquests of which he saw, and in the knowledge that his blows against malaria counted in the attacks upon this drastic system.

The political enemies of Thomas Jefferson protested that in the Louisiana Purchase the United States acquired a swamp unfit for human habitation. The Mississippi Valley is to-day the home of millions. Who will say that the introduction and distribution of quinine in the early days was not a factor of great significance in establishing homes and settlements in a region infested with malaria? The control of malaria in the great valley required years of persistent effort under the hardships of frontier life and was not spectacular; was it less of a contribution to civilization than today's triumphs of sanitation for which we are justly proud?

CINCHONA CULTURE IN JAVA: ITS HISTORY AND DEVELOPMENT

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In 1589, one of the last survivors of the Spanish Conquistadores of Peru, Marcio Serra de Lejesama, wrote a most remarkable confession to King Philip II: "Your Majesty must understand," he writes, "that my reason for making this statement is to relieve my conscience, for we have destroyed the Government of this people by our bad example. Crimes were once so little known amongst them that an Indian, with 100,000 pieces of gold and silver in his house, left it open, only placing a little stick across the door, as a sign that the master was out, and nobody went in. But when they saw that we placed locks in our doors, they understood that it was from fear of theft."¹

That the old Incas should have such confidence in those who passed their dwellings is not only a proof of the general honesty of their fellow citizens but must also chiefly be taken as a proof of the relatively small value which gold possessed in the immured economic state of the Incas before the Spanish invasion. And if the writer of the above-mentioned confession could have foreseen that not only the gold but also a treasure of much greater value, namely, the precious remedy cinchona bark, would permanently disappear from Peru, he would perhaps have made his confession in somewhat different words. However ideal the condition of national honesty of the old Incas may appear, it is certainly better, in view of the "sacra auri fames," to preserve and cultivate the most precious gifts which nature has bequeathed to mankind, so that they may be used for the good of as many people as possible, rather than to leave them to reckless exploitation.

To a certain extent it may be said that the treasure of cinchona bark in the primeval forests of Peru and Bolivia was as inadequately guarded as the gold in the dwellings of the ancient Incas. The Jesuits, it is true, did their best to convince the

¹ Markham, C. R., *Travels in Peru and India*. 1862.

Indian bark collectors that they were morally compelled to plant a young cinchona shoot in the ground for each tree they cut down. Also the Government of Bolivia subsequently attempted to restrict the extermination of the cinchona by legal regulations. But owing to the pressure of rapid exploitation of this most profitable product of the forest, stimulated as it was by the constantly growing demand for cinchona bark, neither the well-meant advice nor the later legal regulations could be more than "a little stick across the door."

For a space of more than two centuries the unbridled exploitation of cinchona growing in its natural forests went on, and although the danger of its extermination had already been emphatically pointed out by men of great authority, such as de la Condamine and von Humboldt, it took many decades for the conviction to become general, that the enormous store of cinchona bark in the South American forests was in danger of becoming exhausted. This danger was even increased owing to the fact that after the discovery that quinine was the most active febrifugal component, the commercial world had learned to value cinchona bark according to the percentage of quinine it contained, and that from the analyses it appeared that the importation of high percentage barks from South America was constantly diminishing.

It is chiefly due to the French savant, Weddell, who visited the cinchona districts from 1843 to 1848, that efforts were eventually made to preserve the cinchona from total extermination by attempting to introduce this plant in other tropical regions. In his '*Histoire naturelle des Quinquinas*' (Paris, 1849) he emphatically pointed out the necessity of attempting to produce cinchona bark in regular plantations if the world were not to lose a medical remedy which had already become indispensable. "Reste la ressource de la culture," he writes, "et il faut l'employer.—S'il est un arbre digne d'être acclimaté . . . , c'est certes le Quinquina; et la postérité bénirait ceux qui auraient mis à exécution une semblable idée."

In one respect, however, Weddell's statement was not complete. It is not only those who carried out Weddell's idea, but also the indefatigable promoters and propagandists of this

idea to whom the gratitude of later generations is due. Therefore Weddell's name will remain one of the first and greatest to which this grateful remembrance will be paid.

When in the year 1852 the Netherlands Government determined to attempt the transfer of the cinchona from South America to Java in order to cultivate it if possible in regular plantations, it was certainly not the calculations of a possible financial profit which induced them to make such a resolution. On the contrary, considerations of a more idealistic nature ranked first in every way. The whole object was to preserve for future generations a medical remedy which had become indispensable, and to make it possible to obtain it regularly in adequate quantities. "Il s'agit, pour ainsi dire, de procurer son pain au malade, et de le lui procurer à des prix qui ne surpassent pas ses moyens. Ce n'est comme spéculation, c'est comme acte humanitaire que le Gouvernement Néerlandais a entrepris et poursuivi cet oeuvre." With these words Rochussen, Governor General of the Netherlands East Indies, most correctly described the motive which led to the transplantation of the cinchona.

The actual reason that far-seeing men of science had urged the transplantation of the cinchona was the danger of a scarcity of the bark and the wish to insure a permanently adequate production of it by regular cultivation. The same motives prevailed when the Netherlands and the British Governments determined to attempt to transplant the cinchona to their colonies.

Without entering into details, I may briefly record here the two expeditions to South America, namely, the Dutch expedition in 1852, and the English one in 1860, sent out with the object of collecting as many cinchona plants and seeds as possible in order to transfer them to Java and to British India respectively.

Instructions to collect and transfer cinchona plants and seeds to Java were given by the Dutch Government to the botanist, Justus Carl Hasskarl, who had already been employed in the service of the Netherlands East Indian Government in the botanical gardens at Buitenzorg near Batavia. Hasskarl left for South America in December, 1852, and he remained there until August, 1854. He succeeded in collecting live plants and

the seeds of several varieties of the cinchona. Of the 500 plants shipped in Wardian cases only 75 proved to be alive on arrival at Buitenzorg. From the seeds brought by Hasskarl and from those which had been previously sent by him, a great number of plants were later obtained.

The leadership of the British expedition to South America was entrusted to Sir Clements R. Markham. As Markham had not studied botany, he had secured, to carry out his enterprise the collaboration of a number of scientific men, several of whom were already more or less acquainted with the cinchona regions after a personal sojourn there. His collaborators were Dr. R. Spruce, Mr. R. Cross, Mr. J. Weir, and Mr. Pritchett. The success of the expedition was chiefly due to Spruce and Cross; together they explored the district of the "red bark," viz., the western slopes of the Chimborazo, and ultimately succeeded in delivering in British India more than 450 live plants and about 100,000 seeds of *C. succirubra* which, besides being the producer of pharmaceutical barks, has become of extraordinary importance as the base on which to graft the *C. Ledgeriana* varieties.

Very soon after the cinchona seeds and plants had been received from South America, British India and Java exchanged varieties for those they lacked, so that early in the sixties both countries possessed a fair number of cinchona varieties, of which the principal were: *C. lancifolia*, *C. cordifolia*, and *C. Trianae*, from Colombia; *C. succirubra*, *C. officinalis*, *C. micrantha*, and *C. Pahudiana*, from Chimborazo, Loxa, and Huanuco; *C. calopera*, *C. Josephiana*, and *C. Calisaya*, from Carabaya. The successful transplantation of the cinchona was followed by a period of researches and experiments for the proper ways and means of propagating the new plant, a period with which the names of Anderson, MacIvor, Teysman, Junghuhn, de Vry, and van Gorkom are honourably connected.

On the island of Java, where we shall now more particularly follow the development of the cultivation of Cinchona, it appeared that with but few exceptions all varieties of *Cinchona* thrived more or less favourably. The new culture succeeded best on the plateau of Pengalengan and on the foothills of the neighboring mountains, a district which had been pointed out

by Junghuhn as being especially suitable for the cultivation of cinchona.

By further shipments new quantities of seeds came from South America to Java, and so the number of plants available increased rapidly, especially as the planters soon learned to propagate the most important varieties in many thousands by means of cuttings. After many dangers and sacrifices in transferring the Cinchona and after much devotion in tending the experimental plantations, it appeared as if the cultivation of the tree in Java could look forward to a splendid future, and yet, without a fortunate accident, the cultivation of cinchona in Java could not have developed and attained the great economic importance which it now possesses.

After a number of years, when the oldest cinchonas had grown to such an age and size that they could furnish sufficient quantities of bark for analyses, all the imported varieties proved to possess a low percentage of quinine, with the sole exception of *C. officinalis*. It was this variety, however, in which the growth was least favorable, and therefore the prospects that it could be used for planting on a large scale were poor. Since the discovery by Pelletier and Caventou medical science had found quinine to be the febrifugal component "par excellence" of the cinchona bark and began to prescribe it to a greater and greater extent; consequently there was a constantly growing demand on the market for cinchona barks of a high quinine percentage. The barks with a low quinine percentage supplied only a small quantity of this product, and for the quinine manufacturers these barks were also objectionable because their relatively high percentage of total alkaloids rendered the preparation of pure quinine more difficult.

And yet sufficient attention had been paid to the importation and propagation of the good varieties from the very beginning. For a number of years previously the Calisaya barks had been by far the most appreciated kind in the cinchona bark trade, and consequently great attention had been devoted to the importation and propagation of this variety. At that time the planters in Java possessed four Calisaya varieties which were classified as follows according to their origin:

<i>C. Calisaya</i> var. <i>javanica</i>	{ Descendants of the first cinchona plant received from the Botanical Gardens at Leiden in 1851. This plant was grown from seed collected in South America by Weddell.
<i>C. Calisaya</i> var. <i>javanica</i>	{ Descendants of seeds and plants collected in South America by Hasskarl.
<i>C. Calisaya</i> var. " <i>Schuhkraft</i> "	{ Plants grown from seed collected in North Bolivia and received through the Dutch Consul at La Paz, Mr. C. N. Schuhkraft.
<i>C. Calisaya</i> var. <i>anglica</i>	{ Grown from seed received from British India.

That the percentage of quinine found in these varieties was not very high, will be seen from the following figures:²

Variety of Cinchona bark	Type of alkaloid content				
	Quinine	Cincho- nidine	Kini- dine	Cincho- nine	Total alkaloids
<i>C. Cal. javanica</i> , trunk bark I	1	0.5	0.3	1.1	3.8
<i>C. Cal. javanica</i> , trunk bark II	0.7	0.2	0.2	0.8	2.5
<i>C. Cal. javanica</i> , root bark	1.2	1.	0.4	1.9	5.2
<i>C. Cal. "Schuhkraft"</i> , trunk bark I	1	0.3	0.5	1.6	4.
<i>C. Cal. "Schuhkraft"</i> , trunk bark II	0.3	0.2	0.1	0.7	2.
<i>C. Cal. "Schuhkraft"</i> , root bark	1.2	0.7	0.2	2.3	5.
<i>C. Cal. anglica</i> , trunk bark I	1.5	1.3	0.1	2.1	5.7
<i>C. Cal. anglica</i> , trunk bark II	1.	1.2	0.1	1.4	4.6
<i>C. Cal. anglica</i> , root bark	1.5	1.7	0.	3.1	6.9

	Extremes of alkaloid content			
	Quinine	Cincho- nidine	Kini- dine	Cincho- nine
<i>C. Cal. javanica</i> , trunk bark I	0-4	0-2	0-3	0.3-2
<i>C. Cal. javanica</i> , trunk bark II	0.2-0.8	0.1-0.3	0.15-0.25	0.7-1
<i>C. Cal. javanica</i> , root bark	0.7-2.1	0.8-1.5	0.3-0.5	1.6-2.5

Although the object aimed at, viz., the preservation of the Cinchona from extermination, had to a certain extent been attained, it did not appear, at least for the present, as if its cultivation in Java would prove to be an economic success, since

² From Moens, J. C. B. De Kinacultuur in Azië, 1882. p. 269.

the barks with a high percentage of quinine, which the market demanded, could only be produced in insignificant quantities.

In the meantime, however, a new variety of *Calisaya* seeds had been received from Charles Ledger in 1865. This seed had been collected by him in the forests of the province of Caupolican in northern Bolivia through information supplied to him by an old Indian bark collector, named Manuel Incra Mamani. The story of the collection and the subsequent adventures of this kind of seed is too romantic not to be recalled here in a few words.

Charles Ledger was an Englishman who had been in Peru and Bolivia since 1836. He had also been engaged in the cinchona bark trade. Encouraged by the expeditions of Hasskarl and Markham, he determined to collect *Calisaya* seeds himself, with the intention of offering them for sale to the British Government. Thanks to his many years' experience and knowledge of the country and its people, especially in southern Peru and Bolivia where the *Calisayas* were to be found, he was the very man to carry out such a task successfully. Moreover, he could also count on the very reliable support of his Indian servant, Manuel, who had formerly been a bark collector and who possessed considerable knowledge of the origin and value of the varieties of cinchona bark.

In the year 1861, Ledger ordered this Indian servant to collect seeds of the best *Calisaya* varieties in the forests of northern Bolivia. It was in 1865, however, before Manuel returned with a quantity of seeds which he had collected from about fifty trees in the neighborhood of the valley of the Rio Mamoré in the Bolivian Province of Caupolican. Markham relates that Manuel had not been able to collect seeds before, because in the four preceding years the flowers had been repeatedly destroyed by frost during the month of April.

Ledger sent these seeds to his brother, Mr. George Ledger, in London, with instructions to offer them for sale to the British Government. But when the negotiations with the officials in London were not successful, George Ledger began to fear that the seed would lose their germinating faculty and therefore offered it to the Netherlands Government, which purchased one pound of it. This was immediately sent to Java, while

Ledger's remaining stock of thirteen pounds was sold shortly afterwards to a British Indian planter who exchanged it with the British Government for *succirubra* seed.

The seed purchased from Ledger by the Dutch Government was received at the Government Cinchona Plantation, in December, 1865, and was taken great care of by the then Director of the Plantation, Mr. K. W. van Gorkom. Although a large proportion of the seed had been spoiled, about 20,000 seeds germinated, and of these about 12,000 plants were planted out in the open somewhat more than a year later. In the year 1872 the first analyses of the barks of the Ledger cinchonas were made in Java.

Up to this moment there had been no reason whatsoever to expect that those *Calisaya* varieties of bark would produce a particularly high percentage of quinine. The first analysis showed, however, that the bark of the Ledger cinchona excelled all other varieties, including those of the other *Calisayas*, considerably in the percentage of quinine. In the report of the Government Cinchona Plantation for that year the Director, Mr. J. C. Bernelot Moens writes: "This variety of cinchona bark is not only remarkable for the high percentage of quinine but also for the facility with which the quinine crystallizes as sulphate."

As the bark of a greater number of Ledger plants was analyzed, higher and higher percentages of quinine were found. The highest percentage in the Ledger bark in 1872 was 8 per cent; 11 per cent was found by Moens in 1874, and in the annual report for 1876 we find the statement: "The proportion of 13.25 per cent of quinine, which has certainly never been found in cinchona bark, is extremely remarkable."

With the increasing amounts of quinine found by analyses of Ledger trees, the Government Plantations in Java grew more and more exacting with regard to the qualities of the Ledger trees from which seeds and cuttings should be collected. It is interesting to record here what was mentioned on this subject in the subsequent annual reports of the Government Cinchona Plantations:

1873.—"Fresh plants will in the future only be grown from

seeds of trees containing more than 5 per cent of quinine in their bark."

1875.—"If the bark contains less than 7.5 per cent of pure quinine, the tree is disqualified for seed production purposes."

1877.—"On the Government Plantations seeds of trees which contain 9 to 10 per cent or more quinine in their bark will in future only be used."

1879.—In this report Mr. Moens states that more than 1000 grafts were made with cuttings from Ledger trees with the highest quinine percentage, including 100 cuttings from tree No. 67, which contained 13.5 per cent of quinine.

The significance of these figures becomes clear when we consider that, before the discovery of the Ledger barks, the other Calisayas with an average percentage of 1 to 1½ per cent quinine were considered to be the best quinine producers and that the other cinchona varieties, with the exception only of the poor-growing *C. officinalis*, as a rule only contained 0.5 to 1 per cent quinine.

The difference between the Ledger cinchonas and the remaining cinchona varieties is even perhaps more striking when we compare the prices obtained at the bark auctions. On the 17th of April, 1877, a cinchona bark auction was held in Amsterdam, at which the Government barks were sold at the following prices:

	per kilogramme
Ledger cinchona barks	F. 17.58
<i>C. Calisaya javanica</i>	F. 4.92
<i>C. Hasskarliana</i>	F. 4.78
<i>C. Calisaya</i> "Schuhkraft"	F. 3.80
<i>C. succirubra</i>	F. 3.36
<i>C. caloptera</i>	F. 3.18

When the first analytical results of the Ledger cinchona barks became known, the Netherlands Indian Government had already, during the previous 20 years, established many experimental plantations. The laying out and maintenance of these experimental plantations and also the transference of plants and seeds into Java had cost much time, labor, and money which, until that moment had shown no prospect of a reasonable profit.

Nevertheless, the Government continued the experiments with great perseverance, in spite of the fact that the public, not appreciating the ideal significance of the work, frequently expressed their dissatisfaction regarding the costly Government Cinchona Plantations. "In the East Indies," Mr. van Gorkom writes,³ "the public ridiculed the expensive hobby of the Government in maintaining a cinchona plantation which after so many years had not shown any prospect of results in hard cash and of which only negative results could be expected. The cultivation of cinchona was looked upon as a hobby of the Governor Generals', who rapidly succeeded each other. Private persons or companies could not be induced to make experiments with the cultivation of cinchona."

It was amazing to see how swiftly all this changed after the discovery of the value of the Ledger cinchona, and particularly after it had been proved that the Ledger barks met a ready demand on the open market at much higher prices than the other varieties of bark. Private enterprises soon exhibited a growing interest in the new culture and gratefully accepted the generous offer of the Government to supply them with seeds and cuttings of Ledger cinchona without charge, if they were prepared to devote their land to its cultivation. There were, consequently, in a very short time a number of private cinchona plantations besides the very large plantations belonging to the Government.

Relying on the experience of the Government estates, the planters sought out for these plantations soils of porous structure with much humus and of recent volcanic origin. Such lands at a suitable height above the level of the sea were chiefly found in the Preanger Regencies on the slopes of the volcanoes and on the plateaus between them, all of which are covered with the fertile soil formerly thrown out by these volcanoes. This explains why the cultivation of cinchona is chiefly concentrated in the mountainous districts of the Preanger. Of 127 cinchona estates on the island of Java, 85 are in the Preanger Regencies, and these together produce almost 75 per cent of the total Java crop. The most important producing district is certainly the plateau of Pengalengan and its surrounding mountain slopes.

³ Scheikundige Bijdragen tot de Kennis der Java-kina, 1872-1907. (1908).

In this way has the cinchona cultivation in Java developed within a few years after having become acquainted with the Ledger cinchona from "a costly hobby of the Government" to an economically profitable agriculture on a large scale, employing thousands of hands and relieving millions of sufferers from malaria, bringing them healing and new life.

If the Netherlands Indian Government has contributed largely to the extension of the cultivation of cinchona by supplying on a large scale seeds and cuttings gratis, in no less degree is the rise of Java cinchona culture due to the special care devoted by the Government plantations from the very beginning to the quality of the planting material. The cultivation of cinchona owes an immense debt to the insight of Mr. J. C. Bernelot Moens, then Director of the Government Cinchona Plantations, who selected for the production of seeds exclusively trees with the highest percentage of quinine in their bark.

Mr. J. Elliot Howard of London, the well-known quinologist, to whom Mr. Moens had communicated the results of his research and told of his plans, wrote to him in 1875: "I commend very much the pains you have taken in this respect and think you will reap the advantage by keeping considerably ahead of all other growers of cinchona." More literally perhaps than Mr. Howard intended, his prophecy has since been realized. For many years past the Netherlands Indian Cinchona Plantations have produced more than 95 per cent of the total world production.

Now since the importation of the Ledger cinchona brought about a complete revolution in the Java cinchona cultivation, there is every reason for us to inquire whether further particulars could not be ascertained as to the special qualities by which the Ledger cinchonas are distinguished from the ordinary Calisaya plants. It will also be interesting to see what has been done in Java to retain and improve these qualities, in so far as they are of importance for the cultivation and production. Generally speaking, the Ledger cinchona is distinguished from the other Calisayas by two features, viz., the botanical and the high quinine percentage.

With regard to the botanical feature, Mr. Howard looked upon the Ledger cinchona as the original form of the genuine Calisaya

and has given it the name of *Cinchona Ledgeriana*; Mr. Moens was of the same opinion and expressed the probability that *C. Calisaya*, which had been found by Weddell in the same district, had been produced by hybridization of *C. Ledgeriana* with other species of *Cinchona* (*C. Josephiana*?). Since experience in the plantations of British India and Java has shown how extraordinarily easy it is for various cinchona varieties to hybridize, it may be safely assumed that hybridization has frequently taken place in the original habitat, and so Mr. Moens' explanation seems to be very acceptable. In any case it is certain that the plants obtained from the imported seed of *C. Ledgeriana* were far from being homogeneous. In the first place, Mr. Moens soon had to distinguish two varieties which differed chemically from the ordinary *C. Ledgeriana*, viz., A, *cinchonidinifera*, and B, *chinidinifera*, characterized by a particularly high percentage of cinchonidine and quinidine respectively.

It further appeared that in the ordinary *C. Ledgeriana* plants very considerable fluctuations occurred as regards the percentage of quinine; for instance among the eight trees which were analyzed in 1872, one of them was found to contain only 4.16 per cent quinine, whereas the highest percentage was 8.15 per cent. In 1876, thirty-four Ledger trees were examined, the highest percentage of quinine being 13.25 per cent and the lowest 6.61 per cent.

Further, it appears that among approximately 200 trees still living of the original trees of *C. Ledgeriana*, very great differences occur both in habit or outward form and in the chemical composition of the barks. The differences in chemical composition came to light a few years ago when all the original *C. Ledgeriana* trees now still living were again sampled and analyzed.

In the table given below are collected the results of the analyses of 155 original trees of *C. Ledgeriana* in the District of Tjinjireean of the Government Cinchona Estates. As is shown by the figures the extreme differences in percentages are very great, viz., from 2. to 6.8 per cent.

Finally, we may also record Mr. Moens' observation that among the descendants of the original Ledger trees there are many specimens which deviate from the type of the mother trees

QUININE CONTENT OF 155 ORIGINAL LEDGERIANA TREES
60 YEARS OLD

Quinine content (per cent)	Number of trees
2 -2.3	4
2.3-2.6	5
2.6-2.9	7
2.9-3.2	11
3.2-3.5	13
3.5-3.8	18
3.8-4.1	28
4.1-4.4	27
4.4-4.7	15
4.7-5.0	14
5.0-5.3	4
5.3-5.6	2
5.6-5.9	2
5.9-6.2	2
6.2-6.5	2
6.5-6.8	1
	155
Average percentage: 3.99	

and exhibit very great likeness to Weddell's description of *C. Calisaya*. For this reason also Mr. Moens concluded that hybridization had taken place in the original forests.

There is consequently every reason to believe that the first generation of *C. Ledgeriana* in Java was already hybridized to a greater or lesser extent, and this fact should certainly be taken into account if one wishes to obtain a correct appreciation of the results obtained from the Ledger seed.

Immediately after the results of the first analyses of Ledger barks had been received, Mr. Moens formed a very clear picture of the further methods to be adopted, which briefly may be described as follows:

1. Seeing that quinine in the sphere of medicine had been found to be the active component of cinchona bark and that medical practice had learned to apply it, an increasing demand for this alkaloid was to be expected; the Ledger barks now proved to be the ideal raw material for the manufacture of quinine, and the cultivation of this variety of cinchona should therefore be energetically pushed.

2. The future Ledgeriana planting material should be improved as much as possible by logical selection.

It is due to the insight of Mr. Moens on both these points that

the Java cultivation of cinchona largely owes its rise and its present important position.

No further explanation need be given as to the first point. The general application of quinine as a remedy for malaria and the indispensability of cinchona bark for its manufacture are now of common knowledge, and this forms the best evidence of the correctness of Mr. Moens' insight.

With regard to what has been done to improve the *Ledgeriana* planting material, I shall now briefly mention a few facts.

It must therefore be remembered that after experiments covering many years the cultivation of cinchona in Java had practically reached an impasse, because only barks with a very low percentage of quinine could be produced; it was only after the high percentage *Ledgerianas* had been secured that the cultivation of cinchona could develop and flourish in a brief space of time.

If we bear in mind this historical development of affairs, it will be perfectly intelligible that for selecting the best plants from the available *Ledgerianas*, the qualities taken into account in the first place were those which distinguished this variety from the other cinchona varieties, viz., 1, the high percentage of quinine, 2, the botanical features.

Trees were therefore selected which in outward form or habit resembled as much as possible Mr. Moens' description of *C. Ledgeriana* and which in addition excelled in possessing a high percentage of quinine. As a rule the method adopted was to take grafts from these selected trees. These grafts were then planted out in a properly isolated field where hybridization with inferior kinds of *Cinchona* was impossible, so that one would eventually be able to collect from these isolated gardens seeds that were due exclusively to mutual fertilization of *Ledgerianas* with a high percentage of quinine.

It is to this method, introduced and applied on the Government Cinchona Estates, that the Java cinchona industry owes its constant supply of good seed, and the fact that the excellent quality of the original *Ledgeriana* seed has not only been retained but also considerably improved.

From among the original *Ledgerianas* two trees were selected

with a high percentage of quinine. From these trees (Nos. 23 and 38), seed (A) was taken and from the descendants obtained from this seed the trees possessing the highest percentages were again selected. These were multiplied by means of grafts and planted out in an isolated seed garden. The seed produced in this garden we will call Seed (B). Now if we compare the yield of the plantations from seed (A) with that from seed (B), we shall be able to draw a conclusion with regard to the effect of the selection. The Government Cinchona Estates now actually possess such figures, and from these figures it has appeared that the plantations from seed (B) produce about 25 per cent more quinine than those from seed (A).

Although results of considerable importance were obtained, it cannot be denied that the method adopted possessed in one respect a serious defect. The method was too one-sided; it led to excessive attention being paid to the percentage of quinine alone. It is true that in selecting, other factors, such as growing power and thickness of bark, were considered, but these factors were not determined in an exact manner and in the ultimate selection played only an extremely subsidiary part. Practically speaking, it was always the percentage of quinine which determined the selection, and another factor, which is also of the greatest importance for the estimation of the production of quinine, namely, the amount of bark produced, was but little or most inadequately taken into account.

It is obvious that the amount of quinine produced is certainly in proportion to the percentage in the bark, but it is not exclusively determined by the percentage; it is found by multiplication of quinine percentage and bark production. To ascertain the amount of quinine produced, the bark production is therefore a factor of equal importance with the quinine percentage. It is clear that a plantation (A) with lower percentage quinine bark may be able to produce more quinine per acre than a plantation (B) with a higher percentage of quinine, if in plantation (A) the bark production is considerably greater.

In order to be able to estimate the value of a cinchona tree or of a cinchona plantation, we must possess a method by which we can readily assemble facts which will furnish a sufficiently

accurate measure whereby to estimate the quantity of bark and the quantity of quinine which is present at a given moment. Further, the method must be able to register with sufficient accuracy comparatively small changes in the stock of quinine in consequence of treatment, as for instance, manuring, draining, digging, etc.

If we now carefully keep in mind the precise significance of the percentage figure, viz.

$$\text{quinine content} = \frac{\text{quinine quantity}}{\text{bark quantity}},$$

it will be clear that the percentage alone is insufficient to give us a correct estimate of the stock of quinine and of the subsequent changes in this stock, unless the amount of bark in stock is also accurately determined.

For a number of years past we have adopted a method which enables us, in a simple and sufficiently accurate manner, to measure the stock of bark and quinine in the trees or groups of trees and also to estimate comparatively small changes in such stock. In this method the point of departure was the consideration that the quantity of quinine which is present in comparable quantities of bark forms a practical standard of measure for the comparison of the respective producing power. It would take too long to describe this method in detail here. It may be sufficient therefore, I think, to state that this method has proved equal to our expectations and that it has enabled us to secure a better knowledge of the value of the various factors influencing the production of quinine, such as the quality of the soil, manure, selection, etc.

As I have already mentioned, the Netherlands Indies practically supply the total world demand for cinchona bark. Now if we see how this state of affairs, which is frequently described as the "Dutch Cinchona Monopoly," has come about, it will appear that two circumstances have been of preponderating influence, viz., the scientific advice which has from the very first supported the cultivation of cinchona, and the extraordinary perseverance of the Netherlands cinchona planter.

As has already been demonstrated, the cultivation of cinchona

in Java owes a great debt to the scientific insight of Mr. Moens, who not only preserved the *Ledgeriana* material for the future but also improved it in quality. There is not the slightest doubt that the strong position of the culture of cinchona in Java which enabled it to withstand long periods of depression, during which the cultivation was given up entirely in other countries, is greatly due to the possession of planting material and seed derived from selected trees of high percentage quinine.

A great number of experiments were also made on other cultural and technical problems, such as the distance apart at which the plants should stand, the method of working the soil, manuring, etc. Also the fact that a suitable grafting method was soon found on the Government Cinchona Estates has been of great influence in the practical cultivation. Not only by means of this grafting method could the high percentage plants be multiplied and the grafts be devoted to the production of seed in isolated gardens, but also by grafting *Ledgeriana* cuttings on *succirubra* bases one obtained the advantage that on less fertile soils where *Ledgeriana* seedlings would no longer thrive, *Ledger* barks could still be produced. In this way the *C. Ledgeriana* was supplied with the strong root system of the *C. succirubra* which can develop freely even on less fertile grounds and which moreover possesses greater resistance against the dreaded root fungus than the *Ledger* roots.

In this way Science continued to supply to the cultivation of cinchona its support and advice, so that the culture was soon raised to a very high level of technical perfection. The natural result of this was that in Java cinchona culture was better than elsewhere able to resist the periods of depression which were to come and, unfortunately, repeatedly did come.

Instead of the shortage of cinchona bark previously feared, a considerable overproduction was the result of the successful cultivation. The supply of cinchona bark was considerably greater than the demand, with the inevitable effect of a severe drop in price. In the year 1880, for instance, the price of 1 kg. of sulphate of quinine was still \$100, while in 1893, with a constantly growing consumption, this price had dropped to \$7. In

1885 the unit price⁴ was still 25 Dutch cents (10 American cents); in 1890 this price had dropped to 7.5; in 1892 to 1897 to about 4, and in 1895 even to slightly more than 2.5 Dutch cents. At the latter price it was impossible even for the Java estates to continue a profitable exploitation. For the sufferer from malaria the condition hoped for by Rochussen, viz., "*des prix qui ne surpassent pas ses moyens*," had certainly been attained, but the cinchona planter saw his livelihood threatened by market prices which were lower than his costs of production. No doubt many a capable planter who had hoped for a golden harvest from the cultivation of cinchona would sigh with Schiller:

Die Ideale sind zerronnen,

Die einst das trunkene Herz geschwellt.

It is certainly due to the perseverance of the Dutch planter who, with great tenacity, while constantly looking for new ways and means of arriving at a cheaper production, steadily continued and improved the cultivation of cinchona, that cinchona culture was not generally given up, especially since in Ceylon the planters began to convert the cinchona plantations into tea plantations. The position of the Java planters then became even more acute owing to the large quantity of bark which Ceylon dumped on the market for a considerable length of time. If we may justifiably consider the maintenance of a constant cinchona production as of vital importance for mankind in general, then the whole of the world certainly owes a debt of gratitude to the Java cinchona planters for persevering in the cultivation of cinchona at that time in spite of the unfavorable circumstances and in spite of the fact that tea plantations held out better prospects financially. Thanks to their perseverance the production of an indispensable medicine has been preserved for future generations.

The Dutch planter need therefore not pay great attention to the views expressed in articles in periodicals and newspapers in which the so-called Dutch Cinchona Monopoly is discussed in a

⁴ As unit is considered on the cinchona market, a quantity of 5 gr. of sulphate of quinine in the bark (= $\frac{1}{2}$ kg. of bark of 1 per cent of sulphate of quinine). The unit price is the amount in cents in Netherlands currency that is paid for 5 gr. of quinine in the bark, i. e. per $\frac{1}{2}$ kg. of bark and per cent of sulphate of quinine.

manner which as a rule exhibits much unfriendliness but little knowledge of the true state of affairs. The planter himself knows how the Dutch position in the cultivation of cinchona has been created by Science and maintained by perseverance.

It is with great satisfaction that after so much lack of appreciation from persons who are mostly incompetent, he may point to the verdict of Mr. E. M. Mellor,⁵ a well-known pharmacologist, who writes: "The introduction of Cinchona and the struggle to make it a commercial success is a fine example of the indomitable pluck, grit and dogged perseverance of the Dutch. Holland has achieved her success this time by forethought, by research, by taking risks, and by doggedness," although the word doggedness does not point to excessive friendliness.

After Ceylon had given up the cultivation of cinchona in favor of the more profitable cultivation of tea and after most of the private planters in British India had also given it up, as not being sufficiently profitable, the Netherlands Indies remained practically alone as a cinchona-producing country. Consequently, we may say that the so called "Cinchona Monopoly" of the Netherlands Indies has come about in an entirely natural way, the way which led to the "survival of the fittest." When hereafter I am using the word monopoly, I only mean to say that practically the whole world's consumption of cinchona bark is produced in the Dutch East Indies. This is quite different from other monopolies, which in most cases are created by special laws and maintained and strictly controlled by official measures and regulations (tobacco, opium, etc.). The cinchona bark monopoly in the Dutch East Indies has grown exclusively by the natural law that results in survival of the fittest and never has the N. E. I. Government tried to maintain this monopoly by special laws or measures. On the contrary, repeatedly our Government has given its highly selected cinchona seeds to those colonial governments that wished to grow cinchona bark. Consequently, these governments could dispose at once of the best quality of seeds and thus were spared the trouble and difficulties of the work of selection. By doing so, our colonial government clearly showed how largely its standpoint differs from that of a monopolist who

⁵ The countries our drugs come from. Pharm. Jour. II, 1922, p. 327.

tries with all possible means to maintain and strengthen his position, and to guard the fruits of his work for himself.

It may now properly be asked: What obligations does the special cinchona position impose upon the Netherlands Indies? This is a question which cannot be answered before first inquiring in a general manner what requirements may be imposed in connection with the production of an important drug, such as quinine. From a purely theoretical point of view, one may state the desideratum, that every sufferer from malaria, even the very poorest, should be able to obtain a sufficient quantity of quinine without difficulty. From statistical figures, the number of sufferers from malaria in the whole world can be calculated, and therefrom how great the quinine production should be in order to provide all these patients with a complete cure. A typical example of such a method of calculation is found in the report of the eighth session of the Comité d'Hygiène of the League of Nations, held at Geneva from the 13th to the 18th of October, 1926 (Fifth Session on the 16th of October, 1926. Work of the Malaria Commission 250):

Recent statistics compiled by Dr. Andrew Balfour gave the annual figure for the whole world of two million deaths, and the authority of Dr. Balfour was a guarantee that this figure was fairly correct. The death rate being from three to four deaths per thousand cases, it followed that there must be 650,000,000 people suffering from malaria, or a third of the human race. Though this figure might appear to be fantastic and paradoxical, it should be remembered in considering the overwhelming inadequacy of the present resources of quinine. Taking a yearly average of forty grams of quinine per patient, 26,000 tons per annum would be necessary. It was urgent that an international conference should be called in order to examine methods of considerably intensifying the production.

It is obvious that such a calculation as above cited can only be considered as being of theoretical value. The conclusion that the production should be increased to 26,000 tons of quinine per annum is exclusively based on theoretical considerations, and has no connection with the actual requirements demanded of an economical system of production. From a humanitarian point of view, it may be comprehensible that one would like to see the production and distribution of quinine organized in such a manner that the very poorest of sufferers from malaria could obtain this medicine, but it is undeniable that this state of affairs is Utopian.

Millions of sufferers are so poor that their purchasing power is practically nil, or at any rate so small that they would not be able to pay even approximately the cost of production of quinine.

In practice the production of quinine can only take into account the law of supply and demand; the industry cannot produce on the basis of a theoretically desired quantity to be consumed at prices which are far below the cost price. If it is desired that the cinchona planters should considerably increase their production with the absolutely certain prospect that the extra production could only be sold at a considerable loss, then one may say that an economic absurdity is desired.

Cinchona growers in the N. E. Indies certainly will not agree with Dr. Balfour, who thinks that an international committee ought to be appointed in order to see how the production of cinchona bark can be raised considerably. If ever an international committee will take up the matter of cinchona production, the first question to be answered will be the following: How can it be realized that large stocks owned by the cinchona growers at present and also their normal production may be used for the benefit of malaria-stricken countries, while at the same time the cultivation of cinchona is safe-guarded and may be maintained on an economically sound basis?

It is evident that this question deserves to receive the attention of the League of Nations. Nobody who is sufficiently informed about the present situation of the cinchona industry can deny the importance of this problem. Moreover, this question evidently is of the greatest importance where malaria has to be suppressed. All experts agree that whatever other measures may be desirable, a well-conducted quinine treatment for the sufferer is indispensable. I may quote here the resolution of the Malaria Commission of the League of Nations: "The first and most important thing to do in malarious localities is to arrange for the treatment of the disease by quinine."

Each serious endeavor to bring present large stocks of quinine at the disposal of sufferers of malaria in an inexpensive and convenient way must therefore be considered as being of great hygienic importance. On the other hand, it is quite clear that as long as interested parties in the struggle against malaria do

not sufficiently take into account the conditions that make quinine production economically possible, all discussions about lower prices and larger production will be vain and worthless. On this question the Dutch cinchona bark and quinine producers have tried to come into contact with the Malaria Commission of the League of Nations. It has now been arranged that the matter will be discussed by representatives of the Dutch quinine interests and the delegates of said Commission. The Kinabureau has also tried to interest the Health Board of the Rockefeller Foundation on the question of distribution of cheap quinine, and we hope that this large and mighty institution of your country, which has done such splendid work in the struggle against malaria, will decide to put its shoulders to this task. The Dutch cinchona planters and quinine manufacturers, I may declare, will be found ready to give all possible assistance.

For the whole of humanity the continuation of the cultivation of cinchona is a matter of vital importance. Such continuation, however, can only be guaranteed if the cinchona planters are enabled to maintain the industry on an economically profitable basis.

The Netherlands Indies are first under obligation to see that the cultivation of cinchona continues to be an economically possible one, so that it will not eventually, as in Ceylon, be given up for more profitable cultures, and also care has to be taken that any abuse of the monopolistic position should be prevented.

The cinchona planters have attempted to preserve an economically profitable cultivation by means of the Cinchona Agreement. In order to make clear to you this much-disputed agreement, I shall first of all give you a few facts about its origin.

I have already given you some facts with regard to the periods of depression affecting the cultivation of cinchona, during which the price of the bark was so low that the entire industry was in grave danger. The first and principal cause of these periods of depression was the over-production of cinchona bark. The supplies of bark frequently greatly exceeded the demand. It goes without saying that when such a condition of things prevailed it was not difficult for the quinine manufacturers to obtain cheap supplies of bark. This was so much easier because a

certain degree of coöperation between the quinine manufacturers had been reached many years previously. On the other hand, among the producers of the bark any trace of a well-organized coöperation was entirely absent; for many years they had been accustomed to acting each according to his own views, and they steadily continued to overload the market with cinchona bark. No further demonstration is required to prove that under such circumstances the manufacturers were the real masters of the cinchona market and had it in their power to fix the prices practically as they chose, a power which they, as business men, could hardly refrain from using. Consequently, if we compare the price of cinchona bark and that of quinine during that period, we shall as a rule find low prices for the bark and an ample margin between the prices for quinine in the bark and as a ready product.

It is clear that only by the united action of all the producers of bark could an end be made to this condition of uncertainty in the cultivation of cinchona. This unanimity was not reached, however, until the years 1910-1912, when the existence of many cinchona estates had once more been placed in a most critical position, owing to a very low price of bark (average unit price, 3 Dutch cents). Only then did the bark producers, chiefly under the leadership of Dr. H. J. Lovink, then Director of Agriculture in the Netherlands Indies, create a sound organization and adopt the firm resolution to act unanimously and in mutual agreement. The new organization of bark producers opened up negotiations with the quinine manufacturers, which in July, 1913, led to the signing of the cinchona Agreement; after an unequal fight of many years' duration this Agreement at last provided a proper basis of coöperation between the producers and the manufacturers. Until to-day this coöperation has been maintained by fresh agreements, though in a somewhat amended form. The control of the correct execution of this agreement is intrusted to the Kinabureau in Amsterdam. This Bureau consists of six representatives of the cinchona planters and six representatives of the quinine manufacturers, and may be considered as the executive power of the Cinchona Agreement.

From the manner in which the Cinchona Agreement was brought about, it will be clear that there is no question of a

"trust" arising from a desire to exploit a monopolistic position by forcing up the prices; the coöperation between the producers themselves and later on between the producers and the manufacturers grew exclusively from the imperative need of putting an end to the condition of great uncertainty for the bark production, which would eventually have led to a general surrender of the cultivation of cinchona in favor of more profitable crops. Thus "*par droit de naissance*," the main object of the Cinchona Agreement is and will be to insure as much as possible the continued existence of an economically profitable cultivation of cinchona.

We can understand, however, that many an outsider will ask whether the condition thus created by the Cinchona Agreement will not ultimately lead to a purely mercantile exploitation of the favorable monopolistic position. It seems to me that those who argue thus are entitled to a further explanation, because ultimately everything depends upon the manner in which the management of this monopolistic position is conducted.

Seeing that the Cinchona Agreement has existed since 1913, we may first of all ask the question whether in the seventeen years during which this agreement has controlled the cinchona situation it has led to the abuse of the position, in other words, to an unreasonable forcing up of the prices.

When answering this question we must leave out of consideration the period in which, in consequence of the great war, the prices of practically all commodities reached an abnormal level. It would have been very strange if, during this period, a medical remedy which all the belligerents urgently required had not also increased in price.

It may, however, be remembered that, compared with other important medicines, the rise in price of quinine was rather moderate. Moreover, one has to give attention to the fact that during that period, a considerable stock of second-hand quinine existed, and the Kinabureau had nothing whatever to say in the selling price of this stock. The best proof of the fact that the Kinabureau did not take advantage of its favorable position during the war to ask too high prices lies in its war agreement made with the Allied Powers. By this agreement large quantities

of quinine were sold at a moderate price, far below the market price at that time. As an impartial judgment of this agreement, I may quote here from Martindale & Westcott's well-known 'Extra Pharmacopoeia:' "The famous War Agreement saved the situation. The Associated Countries secured practically the whole year's production of Java quinine on reasonable terms."

If we now leave out of consideration the period during which the war has influenced the prices, it will appear that, taking the production cost into account, the prices have fluctuated at a normal rate. Moreover, the prices during the war may be regarded as a compensation for the very bad position before the war, when the prices were much lower than the cost of production.

It is certainly a pity that, owing to the prolonged influence of the war period, figures for a comparatively small number of years only are available, and that the conclusion drawn from them can only be of relative value. Therefore, it is fortunate that there is another fact that gives us every guarantee that the Cinchona Agreement will not be abused for the purpose of forcing up the prices unreasonably, namely, the fact that the Government of the Netherlands East Indies, as the largest producers of cinchona bark, have a preponderating influence in the matter.

At great pains and with great devotion did the Government introduce and encourage the cultivation of cinchona in Java, not for financial profit but "*humanitatis causa*." As far as the economic side of the bark production is concerned, the Government has always adopted the stand that only a reasonably profitable industry can be the sound basis for a normal and constant production. The Government has therefore greatly helped towards the making of the Cinchona Agreement and as a bark producer has become a signatory to this agreement, firmly convinced that the Cinchona Agreement is to be looked upon as an absolutely necessary step to enable the cultivation of cinchona to be maintained as an economically profitable industry. It is absolutely out of the question that the Government, either directly or indirectly, would participate in a measure which would serve as a means of forcing up the price of cinchona bark unreasonably, with an eye to purely mercantile considerations.

The object which originally led the Government of the Nether-

lands Indies to the introduction of the cultivation of cinchona still ranks first, namely, the assurance of a regular production of a medicine which has become indispensable for the whole world, in order to place it within the reach of as many people as possible. This standpoint came out very clearly in 1874, when the Government had to pass a resolution with regard to a petition presented by private cinchona planters asking to buy the Government plantations. The answer then was, that the Government would not give up their plantations, because in Java cinchona was then not yet cultivated on a large enough scale.

The proof that the Government seriously desires to safeguard against any possible abuse is clearly demonstrated in Article 117 of the Cinchona Agreement, which was inserted because the Netherlands East Indian Government made it a condition of subscribing to the agreement. This Article reads as follows: "The Government of the Netherlands East Indies reserves the right to surrender membership of the Association at a year's notice, if the Government is of the opinion that the Cinchona Agreement forms an impediment for the supply of cheap quinine to the malarial districts."

The Government thus made its permanent coöperation to the Cinchona Agreement dependent on the manner in which the supply of cheap quinine is continued to the malarial regions. If in the opinion of the Government this supply of cheap quinine to the malarial regions is impeded by the Agreement, its collaboration in the Agreement will cease.

It will be clear that in this way a most reliable safeguard against possible abuse of the agreement is assured, for without the collaboration of the Government, which controls about 10 per cent of the entire bark production through the Government Cinchona Estates, the Agreement could not be maintained. The supply of cheap quinine has thus indirectly become the *conditio sine qua non* for the existence of the Cinchona Agreement.

That the Kinabureau is quite sincere in its endeavors to distribute quinine at low prices to malaria-stricken countries, may appear from its contracts for the supply of cheap quinine, for instance, with Albania, Bulgaria, Greece, Russia, and Italy. Moreover, Russia was presented with 1,000 kilos of quinine

hydrochlorate a short time after the war when there were many difficulties in that country and there was a great need for quinine. The Kinabureau also has asked for the coöperation of the Protestant and the Roman Catholic missions to bring cheap quinine to malaria sufferers in the most remote parts of the earth, for instance in China and the Belgian Congo.

From a purely mercantile standpoint it will certainly appear strange that a combine, favored by all the advantages of an undisputed monopolistic position, has undertaken to supply its products so extensively at a very low price. As stated, this stipulation was inserted in the Agreement at the express desire of the Netherlands East Indian Government. And yet it is not exclusively due to the preponderating influence of the Netherlands East Indian Government as producers of bark that this obligation was accepted by the parties to the Agreement, but also to the conviction that by accepting this condition they not only fulfilled a duty towards mankind but would also promote a sound development of the cinchona position.

To make this clear I shall now briefly review the main points of the general question of the cinchona production.

The cinchona position is entirely governed by over-production, which is partly due to the extension of the plantations and partly to the more intense cultivation in the last ten years, particularly in consequence of selection and fertilizers.

It is obvious that it is greatly in the interest of the producers that the consumption should be increased, as can, for example, be induced by a systematic supply of cheap quinine to the regions infested by malaria. Their interest cannot lie in a "trust" for forcing up the prices. On the contrary, their interest demands the sale of as much quinine as possible at average prices at which a profitable cultivation can be maintained permanently. It is therefore logical that the producers will coöperate, with a normal sale of quinine, to supply as large quantities as possible at very low prices with a view to the quininization of malarial regions with impoverished populations.

If it is asked what would be the position as to the supply of cheap quinine to malarial regions if the producers and manufacturers were not organized in the Cinchona Agreement, the

answer would most probably be: "Deplorable." In fact, without the Cinchona Agreement, the supply of cheap quinine to the malarial districts would by no means be assured. As was the condition before the war, quinine would then frequently become a speculative article in the hands of middlemen not at all interested in the ethical side of the question of the distribution of an important drug. The trade would then be chiefly interested in the supply of quinine to markets where the largest profits could be made and certainly not in the supply of cheap quinine to impoverished sufferers from malaria. The various governments interested in quinization of malarial regions would then not have the assurance that they could obtain adequate supplies of cheap quinine for many years, a certainty which the Cinchona Agreement now furnishes them. However strange this may sound, it is precisely the much-discussed "Cinchona Trust" which offers the best chance of supplying the malarial regions with cheap quinine.

Ladies and Gentlemen: I hope that in this brief review of the quinine situation I have made it clear that the Cinchona Agreement is by no means an ordinary "trust" but that it should rather be considered as an understanding by means of which an economically profitable cultivation and the supply of cheap quinine to malarial regions is guaranteed on a sound basis.

There was a time when the so-called "Dutch Cinchona Monopoly" was discussed in the press, including the press in this country, in anything but friendly terms, a time during which, thanks to these incorrect press views, it frequently appeared as if the Dutch bark producers were a kind of cinchona usurers. Perhaps it has been an error on our part that we have not previously made the public aware of the history and the true significance of the Cinchona Agreement. I therefore consider it a so much greater privilege, Ladies and Gentlemen, that I have now had the opportunity of putting this more clearly before you.

The remarkable development of your enormous country, whose youthful energy has created so much that is great, has doubtless to no little extent been advanced by the regular production of the Netherlands cinchona plantations. It is due to the supply of sufficient quantities of quinine that in this country you have

been able to develop more rapidly and on a larger scale many regions where malaria prevailed. The Dutch nation is proud that, thanks to the introduction of cinchona cultivation in Java, it has also indirectly been able to help in the great building up of your country. But we Netherlands would also appreciate it if you would realize, and I hope that I have contributed something to this end, how the ideal interests which the cinchona cultivation must serve are well protected against purely mercantile exploitation. We desire that the Dutch cinchona cultivation shall continue to deserve fully the name which was given it shortly after its introduction in Java, viz., a pearl in the crown of the Netherlands!

THE PHARMACEUTICAL PREPARATIONS OF CINCHONA

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The earlier pharmaceutical preparations of cinchona were probably infusions or decoctions, sometimes made with or mixed with wine.

The first U. S. Pharmacopoeia, that of 1820, contains a formula for the decoction—made by boiling one ounce of cinchona bark in a pint and a half of water for 10 minutes, and straining—and formulas for four infusions. The plain infusion was made by digesting an ounce of cinchona in a pint of boiling water for two hours, then straining; the “Infusion with Lime Water” was prepared by rubbing one ounce of ground cinchona with a pint of lime water for 15 minutes, then allowing it to stand one hour, and straining; the “Infusion with Magnesia” was made similarly by rubbing one ounce of cinchona and one drachm of magnesium oxide with a pint of (cold) water for 15 minutes, letting it stand one hour, and straining; and the “Infusion with Lemon Juice,” by macerating one ounce of cinchona in a mixture of two ounces of lemon juice, three drachms of camphorated tincture of opium, and a pint of (cold) water for 12 hours, then straining.

It should be noted that three of the four infusions were made without heat, and that the “Infusion with Magnesia” did not enter the second edition of the Pharmacopoeia, and only the plain infusion survived after the second edition. The plain infusion was continued until the revision of 1900, but was, in the later editions, made by percolating the ground drug with cold water well acidulated with aromatic sulphuric acid. The decoction was continued through six editions, since when no official preparation of cinchona has been made by hot extraction. The British Pharmacopoeia still continues the hot-infusion method, but uses aromatic sulphuric acid in the water.

The tincture in the U. S. P., 1820, was made by macerating six ounces of ground cinchona in two and a half pints of diluted alcohol for 10 days, then straining. The compound tincture was made similarly, using two ounces of ground cinchona, one and a

half ounces of dried orange peel, three drachms of Virginia snakeroot, and a drachm each of saffron and red saunders in a pint and a half of diluted alcohol. It is interesting to note that this compound tincture, which has continued as an official preparation to the present day, still contains the main ingredients of the original formula, viz.—cinchona, orange peel, and serpentaria.

An extract was also official in the first U. S. Pharmacopoeia, which was continued until 1900 and has been included in the National Formulary since then.

It is significant to note that no wine of cinchona has been recognized in American pharmacy, though wine was a very early vehicle for the drug. One suspects that the action of organic acids upon the cinchona alkaloids, by which they are changed to an isomeric form having a different and harsher therapeutic action than the natural alkaloids may have had something to do with the singular opposition to the use of cinchona in its very early days. If preparations were made by heating the drug with wine the change of quinine to quinicine, cinchonine to cinchonidine, etc., was probably quite rapid, and a very different but not understood action might be expected.

Even before the action of organic acids in causing polymerization of the alkaloids was appreciated, there was a consistent avoidance of these in cinchona preparations. The only notable exception has been the elixirs, which were very popular during the middle and later years of the nineteenth century. Lloyd's book on "Elixirs" gives forty formulas for elixirs of Calisaya in various combinations, and while a few of these contain a slight excess of acetic or citric acid the majority were either neutral or alkaline in reaction. The National Formulary still has five elixirs in which cinchona alkaloids are the main agents, and three others containing quinine salts. None of the five contain any free acid, and two of the three contain small amounts, one of citric acid and one of lactic.

None of these elixirs are made with heat, and if change takes place in the quinine it is through aging. The fact that such elixirs darken in color on standing suggests that a change in the character of the alkaloids may take place, but if so the change is doubtless very slow under ordinary conditions.

Cinchona has been administered in most of the pharmaceutical forms of medication. Beside the common forms of tincture, fluid extract, extract and elixir, it has been administered in the form of syrup, glycerite, wine, hot and cold infusion, decoction, mixture, tablet, electuary, suppository, and even in poultice. Detannated tincture or fluid extract is still used to some extent, but is chosen chiefly to avoid the darkening when mixed with iron salts that results from the official preparations. The wine has not been greatly used, probably because of the action of the organic acids on the alkaloids, but some formulas have offset this by adding hydrochloric acid, to the sacrifice of palatability. But palatable preparations of cinchona are still more of a dream than a reality.

The pharmaceutical preparations of cinchona in use at the present time are mainly the tincture, compound tincture, and fluid extract. There are smaller amounts of extract and of detannated fluid extract or tincture in use. The decoction has disappeared from American pharmacy, and the infusion is rarely used. These preparations are all made from cinchona bark by extraction with a suitable menstruum. Elixirs and ampul solutions are made from the alkaloids and are not here considered further.

That cinchona is a particularly difficult drug to extract has long been recognized and the question often studied. Since the standardizing of alkaloidal preparations has become general, this peculiarity has received much attention, first in regard to the alcoholic strength of the menstruum, and later with respect to the use of acid.

The earlier tinctures and fluid extracts were made with diluted alcohol. This serves fairly well for extraction but precipitation was voluminous in these preparations. Increasing the alcoholic strength reduced the amount of inert extractive in the preparation and so reduced precipitation. The present official fluid-extract menstruum is 77 per cent alcohol (alcohol 4 volumes, water 1 volume), and that of the two tinctures is 64 per cent alcohol (alcohol 2 volumes, water 1 volume). There is no material difference in efficiency in extraction between these two menstrua, but the weaker one extracts more inert material and so results in greater precipitation.

A menstruum of higher alcoholic strength than 77 per cent (by volume) does not exhaust the drug as well. This therefore seems to be the most desirable strength for these preparations. But since a neutral menstruum produces a preparation that will precipitate freely, it is not satisfactory. While the precipitate consists largely of inert material, yet it carries down with it some of the active alkaloids and so weakens the preparation.

Acid, used in the first portion of the menstruum, greatly improves it. There are two reasons for this: first, the alkaloids are more soluble in an acidulated menstruum, and second, the tannoids are less soluble.

The peculiarity of cinchona lies in the fact that its active constituents, the several alkaloids, are associated in the drug with tannoid bodies, and these are chemically antagonistic. They tend to combine and form insoluble bodies.

Acids hinder, or prevent, such combinations and so promote both extraction and stability. Organic acids are not suitable because they promote the polymerization of the alkaloids into bodies having a harsh and very different therapeutic action. Mineral acids, on the contrary, stabilize the alkaloids and prevent such changes, even in the presence of organic acids. Since the hydrochlorides and acid hydrochlorides of the cinchona alkaloids are more soluble than the sulphates or acid sulphates, hydrochloric acid has proved to be the most effective acid to use. Fortunately it also hinders the extraction of the tannoids and reduces the amount of inert extractive in the preparation, so preventing precipitation. Hydrochloric acid therefore exercises a three-fold function. It promotes the solubility of the alkaloids, thus favoring extraction; it decreases the amount of inert extractive in the preparation, thus increasing pharmaceutical stability, and it prevents the polymerization of the alkaloids, thus insuring therapeutic stability.

The method of use and the amount of hydrochloric acid are important. The first is easily settled, but not so the second.

Since the acid probably acts by forming acid salts of the alkaloids its concentration in the first portion of the menstruum used produces the best results. For the Calisaya type of cinchona an amount of acid equivalent to 1.5 to 2 per cent of hydrochloric acid has

proved most efficient. This is for a bark containing 6 to 9 per cent of total alkaloids. Richer barks require more acid, and a concentration of 3 per cent of acid in the menstruum for the moistening and first maceration may be more effective in these. A material excess of hydrochloric acid is, however, objectionable.

The amount of tannoid material in the drug influences the action of the acid. Since hydrochloric acid changes the tannoids into insoluble phlobaphenes, and this change is accelerated by increase in acidity and by heat, it seems probable that some of the acid is used up in this way. Tests have shown that a cinchona which is rich in both alkaloids and tannoids requires about 3 per cent of acid, but that 4 per cent materially reduces the rate and amount of alkaloids extracted. Furthermore, the acid must be used in the first portion of menstruum only, preferably in that portion used for moistening the drug, because if the weaker portions of percolate, which are later concentrated by distillation, contain any material amount of acid the heat causes a more liberal formation of phlobaphene and this occludes alkaloids, thus causing a loss.

It is therefore impracticable to direct a definite optimum amount of hydrochloric acid for use with all strengths and varieties of cinchona, because of the great variations both in alkaloids and tannoid content. A preliminary assay for alkaloidal strength would be a help in calculating the amount of acid to be used on any particular sample, but the tannoid content must also be taken into consideration, and one can only judge roughly of that since there is no practical method of determining the tannoids accurately.

Rapid extraction is of great advantage with cinchona. Pharmacists have been so strongly habituated to long macerations and slow percolation that to suggest rapid extraction, and that for a drug which has given especial trouble to exhaust, sounds like heresy. Nevertheless, experience has shown its wisdom, and better results are obtained by a short maceration and a rapid flow.

The reason is clear when one considers that the especial function of hydrochloric acid (for rapid extraction is advocated only when hydrochloric acid is employed) is to make the alkaloids more quickly and easily soluble and at the same time to hinder the solution of the tannoids. A short maceration and relatively

rapid flow then provides a better separation of these two, and results in a more stable preparation as well as economy of time.

Stability in the fluid preparations of cinchona is secured by regulation of the alcoholic strength, by the presence of hydrochloric acid, and by the use of glycerin.

The first consideration for procuring a stable preparation is to employ a menstruum which will be effective in exhausting the drug of its alkaloids but will extract but little of the tannoids and will also prevent hydrolysis of the latter. A 77 per cent, by volume, of alcohol has proved to be the most efficient strength both for exhaustion and for hindering hydrolysis. Its especial advantage over lower strengths of alcohol lies in its anti-hydrolytic property.

Hydrochloric acid, as before stated, acts somewhat surprisingly in rejecting the tannoid bodies while aiding in extracting the alkaloids. This is probably the main reason for its efficiency in preventing precipitation. But it also probably acts in some degree in preventing the hydrolysis of the tannoids that are extracted. It is also of value in preventing the isomerism of the alkaloids. This is probably of little consequence in the preparations themselves, in which there is little danger of the change unless mixed with organic acids, but it is a safeguard in mixtures. Since mixtures of cinchona alkaloids or preparations with organic acids have become more common some attention to this phase is advisable.

While the alcoholic strength and the use and presence of hydrochloric acid are the main factors in producing stability, the variations in composition and also in extraction of cinchona make it advisable to employ glycerin also to maintain a clear solution. Glycerin is of no value in extraction—in fact it hinders it when used in the menstruum—so is better used in adjusting the final volume. Furthermore its proportion in the preparation should be uniform, which is not the case in the present official preparations. Glycerin probably aids in reducing or preventing hydrolysis, as does alcohol. Sugar or glucose will serve a similar purpose, and almost as efficiently, but in an acid menstruum they are slowly changed into caramel-like bodies which finally precipitate. Glycerin is therefore preferable, and it should be used in adjusting

the final volume of the preparation and so obtain uniformity in composition.

With a change in the rate of extraction and the proper use of glycerin, as indicated above, the pharmaceutical preparations of cinchona should give no more difficulties than other tannoid drugs.

THE MINOR ALKALOIDS OF CINCHONA BARK

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The bark of the Cinchona tree harbors, in addition to quinine, a number of other alkaloids. The quantities of these alkaloids vary with the variety of the cinchona. Even in the same tree they are not uniformly distributed. The bark from the roots will generally have more of these alkaloids than the stem. In Java bark, these alkaloids average in the neighborhood of 2-2½ per cent.

The alkaloids known as "the minor alkaloids of cinchona" are: cinchonine, cinchonidine, quinidine. Java bark contains from ⅓ to ½ per cent of each of these alkaloids. They are recovered in varying quantities during the extraction and purification of quinine sulphate. The processes of recovery and the purification are kept secret, and no doubt vary according to the skill and individual experience of the different manufacturers. Their separation from the residual liquors accumulated during the manufacture of quinine sulphate is complicated and difficult, as in their impure condition the minor alkaloids do not comply with the physical properties of either the alkaloids or their salts in a pure condition. The presence of large quantities of amorphous alkaloids further complicates the processes, so that considerable skill and ingenuity are required in order to isolate the various alkaloids that have any importance, and to present them in a purified state. The principal use of these alkaloids and their salts is for medicinal purposes.

Exhibit "A" represents the precipitated alkaloids from a primary mother liquor of quinine sulphate. Not only is it still rich in quinine, but it contains all the minor alkaloids, including the amorphous alkaloids. After the quinine that remains in it is isolated the cinchonine, Exhibit "B," cinchonidine, Exhibit "C," and the quinidine, Exhibit "D," are removed, the residual amorphous alkaloids are termed chinoidin, Exhibit "E."

Cinchonine— $C_{19}H_{21}ON_2$ —was isolated in its crystal form by von Gomez in the year 1811, although it was not recognized as an organic base until 1820 by Pelletier and Caventou. This alkaloid

is supplied in the form of colorless crystals or as powder, and it does not contain any solvent of crystallization. Cinchonine alkaloid, as well as its isomer cinchonidine (see below), is but slightly soluble in ether. This property is frequently made use of to distinguish it from quinine or quinidine. Solutions of cinchonine rotate plane polarized light to the right.

The "strength" of cinchonine as a base is somewhat below that of quinine, but it forms well-defined salts with many mineral acids as well as with stronger organic acids. The most important salt of it is the neutral sulphate $(C_{19}H_{22}ON_2)_2 \cdot H_2SO_4 \cdot 2H_2O$ which is official in the National Formulary. In appearance it varies considerably from the sulphates of the other cinchona alkaloids, as it does not form the beautiful silky crystals characteristic of sulphates of quinine, quinidine, and cinchonidine.

Cinchonine is distinguished from quinine and quinidine by not yielding, in the pure state, a fluorescent solution with excess dilute sulphuric acid, also, by its failure to give the thalleoquine reaction. Cinchonine of commerce, however, generally gives a slight fluorescence with sulphuric acid.

Cinchonidine— $C_{19}H_{22}ON_2$ —is an isomer of cinchonine. It was discovered by Winkler in the year 1847. The alkaloid crystallizes in beautiful, rather large crystals; it is also supplied as a powder made by precipitation. Neither form retains solvent of crystallization. This alkaloid, like cinchonine, is only slightly soluble in ether. Solutions of cinchonidine rotate plane polarized light to the left, thus differentiating it from cinchonine which rotates to the right. It is also distinguished from cinchonine by forming a slightly soluble tartrate. Of the salts of this base, the sulphate $(C_{19}H_{22}ON_2)_2 \cdot H_2SO_4 \cdot 3H_2O$ is the most important and is included in the United States Pharmacopoeia. Its crystal form is isomorphous with quinine sulphate which makes difficult the complete freeing of quinine sulphate from this alkaloid.

Quinidine— $C_{20}H_{24}O_2N_2$ —is isomeric with quinine. It was first isolated in 1848 by van Heijningen, although it had been previously observed in 1833 by von Henry and Delondre, who erroneously designated it as quinine hydrate. When crystallized from alcohol it is obtained in well-formed monoclinic prisms containing one molecule of alcohol of crystallization which, however,

it loses more or less readily on exposure to air. The alkaloid precipitated from an aqueous solution is free from water. Quinidine and its salt have medicinal uses. The alkaloid is official in the National Formulary, and the sulphate $(C_{20}H_{24}O_2N_2)_2H_2SO_4 \cdot 2H_2O$, which is the most important salt of quinidine, is included in the United States Pharmacopoeia. Solutions of quinidine in excess of dilute sulphuric acid exhibit, like quinine, a beautiful blue fluorescence, and also similar to quinine, give the thalleoquine reaction. This reaction is made by adding a few drops of bromine water to a few cc. of a dilute solution of quinidine, made with the aid of sulphuric acid, then upon adding a slight excess of ammonia water a beautiful emerald-green color is produced. Quinidine is distinguished from quinine by being dextrorotary and by the greater solubility of its sulphate and tartrate.

Chinoidin—Sertürner, in the year 1828, first designated the amorphous alkaloid he isolated from *Cinchona Calisaya* as chinoidin. [Sample exhibited]. The name chinoidin covers a multitude of sins. It consists of the amorphous alkaloids contained originally not only in cinchona bark, but those developed by the decomposition of the other cinchona alkaloids during the process of extraction and purification. The chinoidin of quinine manufacture may be compared to the molasses of the sugar industry.

From a commercial standpoint it would be a great help to the cinchona and quinine industry if extended uses could be found for these minor alkaloids. Although chinoidin has been used as an accelerator in the vulcanization of rubber, this use has not been extended. It is very interesting to note that as a result of the work by Lloyd E. Jackson and Helen E. Wassell at the Mellon Institute of Industrial Research on the mothproofing of fabrics and furs, the use of cinchona alkaloids may find extensive application.

Let us hope that an ingenious student of chemistry may find a useful application for chinoidin as this is being accumulated in ever-increasing quantities by the manufacturers of quinine.

THE CINCHONA ALKALOIDS IN MEDICAL SCIENCE: AND ESPECIALLY THE QUININE-MALARIA REACTION AS A TOUCHSTONE OF CHEMO-THERAPY

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AN APOLOGY

When we meet to-day to celebrate the three-hundredth anniversary of the first-recognized use of cinchona, we are not really celebrating a date of the calendar; we are merely taking advantage of this date to express our appreciation of what cinchona has done for humanity. In order to appreciate this, the benefits must be present in our consciousness, and therefore it is fitting to take stock, as it were, of what civilization owes to cinchona. From the standpoint of the political historian and of the economist, cinchona has conquered empires; has gained and lost military campaigns; has created fabulous wealth—but in the end all these are but reflections of its role in medical science. I had therefore planned to examine what cinchona has meant to medical science: its advent in the dawn of a new civilization; its influence on the revolution in medicine, from the authority of human tradition to that of verified observation; the discovery of definite active principles, the alkaloids; the improvement of drug plants by scientific cultivation; the stimulation of the production of synthetic competitors and where this has led; the relation of chemical constitution and pharmacologic action; the conquest of malaria, founded on empirical experience, waiting for further rational development; the evolutions and involutions of chemo-therapy; allergy and idiosyncrasy; the vast and somewhat vague field of colloidal biology; the meaning of enzymes, metabolism, heat regulation, water-balance, and analgesia; the facts and theories of muscular contraction and refractory period and cardiac fibrillation; local anesthesia and irritation; antiseptics, general and specialized. Through all these I intended to show that the history of cinchona epitomizes the development of modern medical science, because cinchona is so important in medicine that it enters into practically every field of inquiry. However, when I

proceeded with this program, I came to see that the attempt to condense the whole progress of medical science into the frame of an occasional address must tend to confuse the picture, and it seemed better to concentrate upon a few of the most striking features. Just when I had finished writing the address along these lines I received the program. Imagine my horror when I found that all the topics which I had elaborated in my picture formed the topics of the special addresses of the other speakers. The chief piece, the relations of the quinine-malaria reaction to the theories of chemo-therapy, is to be covered in the next address, by Dr. Maxcy, who really knows the subject about which I have only read and dreamed. My first impulse was to write another address, but I lacked the time; and as I turned the matter over in my mind it seemed to me that there might still be some interest in looking on these problems from the general, rather detached point of view which I had adopted. It may be interesting to note how this agrees with the views of the experts who address you. More often, I presume, our views will appear to conflict, because we shall probably be seeing the subject in a different illumination. If I happen to agree with them too much, I beg their forgiveness, and yours.

THE SETTING OF THE STAGE FOR THE DISCOVERY OF CINCHONA: THE NEW CIVILIZATION

The development of our knowledge of cinchona furnishes a sort of epitome, or rather is symbolic, of the history of modern science, its currents, its eddies and its pools, its depths and its shallows, its discoveries and theories and errors, its achievements and checks and failures.

The date of the introduction of cinchona, 1630, coincides closely with that of the major event, the chief turning point, of medical science, the publication of Harvey's work on the circulation, which appeared in 1628. The prime significance of this book was that it dared to turn from the "authority" of tradition to the observation of nature; that it boldly affirmed that the data of observation and experience must take precedence over the dicta of preconceived or transmitted dogmas; that speculations must yield to facts. This is the essence of the scientific method, the

viewpoint which appears self-evident to us and which was quite well understood in the classical antiquity, but which for nearly 1500 years intervening had been completely narcotized or apparently killed, smothered by the obsession of the infallibility of traditional authority. It is difficult for us to understand this medieval point of view unless we realize that it was the root and fruit of an entirely different type of civilization than that founded on individual liberty of thought, in which we have been bred; a type as distinct as is the civilization of Buddhism from that of efficiency engineering. Man is capable of living happily and consistently under various types of civilization until his needs or surroundings become altered, and the particular type ceases to fit, when he begins to feel the need of change, gradually, at first almost unconsciously, till a certain pressure and tension has accumulated. Then, rather suddenly, there is an explosion, with clash of things and thoughts, and a new type of civilization emerges and takes form and there is a "Reformation."

The change from the medieval civilization was initiated largely by the material discoveries of science; the discovery of astronomy, which shifted the center of the universe from the earth to the sun; the discoveries of the new continent, America, with its vast territories and its gold, which shifted the political power of the world; the discovery of gunpowder, which exploded the authority of feudalism. Discoveries such as these could not be fitted into the old civilization, and pointed the need of change. They opened the minds to the new, they created and fostered the will to progress, to adventure, to try and to experiment; they created a class of progressives and encouraged them to battle with the opponents of change, the defenders of the old "order," the reactionaries. In medicine, this revolt of progress was started chiefly by Vesalius, for structure; by Harvey for function; and by Cinchona for therapy. It may be realized, therefore, that the discovery of the cinchona in 1630 fell upon a world which was at least interested, for or against it. It was itself symbolic of the turn of the two civilizations. The bark of Peru upset the "traditional" medicine quite as much as the gold of Peru upset the traditional political balance.

THE DISCOVERY AND INTRODUCTION OF CINCHONA: THE
EMPIRICAL METHOD IN MEDICINE

We lack all knowledge as to how the specific anti-malarial action of cinchona was discovered, and know but little as to how the discovery was first transmitted to the Europeans. It emerged through a Spanish official, Don Francisco Lopez de Cannizares, of Loxa, Equator, who had tried it since 1630 on himself and on others, found it successful, and supplied it to the Countess Chinchon in 1638. From thence the history is complete; but how did Cannizares come to try it? It is not the sort of discovery which a layman who was busily engaged in other affairs would be likely to make for himself. We may suppose that he was told about it by some one who had had experience with it, presumably an Indian; and yet it appears that the Indians were not acquainted with the anti-malarial action. This would be analogous to the discovery of the actions of digitalis and of ergot, which were not in general use, popular and professional, but which were the treasured secrets of some "wise women." Originally they were discovered by chance by some enthusiastic, but rude and reckless experimenter. Occasionally we read of such people now, who try all sorts of poisons on their friends, to see what they will do, and so acquire the power of mysterious knowledge. Several such cases have come to light in Cleveland's foreign districts. This illustrates the empiric method; to try and to observe and to apply what has been learned; and this is a very fruitful method in therapeutics, and often the only method that is successful. The chief drawbacks are, first, that it is too reckless, beginning on the human before it is safe to do so; and second, that it stops too soon and does not fully utilize the fruits of its conquests.

Presumably, then, some individual, probably a "medicine man" (or woman!), with more curiosity than conscience, experimented with the bitter and reputedly poisonous bark in various directions, by the simple method of trial and error, and in this way stumbled upon its action in malaria. He probably kept this as a valuable secret, which increased his power in the tribe, as long as it remained his secret; but for some reason he imparted it to the white chief or trader and the action was so striking and decisive that it could not fail to make its way on a strictly empirical basis,

at least until it struck the School Physicians and collided with their traditional theories.

The reception of cinchona by the best of the leaders of medicine may be illustrated by a quotation from the great Sydenham, written about 1680, some thirty years after the introduction of cinchona into England. The citation shows the prejudices which faced the new agent; but it is also remarkable for the penetrating observations and deductions which anticipated many of the later discoveries of chemo-therapy. The remarks are part of a long letter or "Epistle," on the subject of the 'Epidemical Diseases from the Year 1675 to the Year 1680,' written probably early in 1680 to Dr. R. Brady, "the King's Professor of Physick in Cambridge," cited from the eighth edition of John Pechey's English translation of 'The Whole Works of that Excellent Practical Physician, Dr. Thomas Sydenham, London, 1722.' The discussion of the treatment begins as follows:

As to the Cure, it has now been well known to me for many Years how dangerous a thing it is in Tertians and Quotidians (which when they are new, and have put on no Type, are still next door to continual Fevers) to attempt the removal of them by Sudorifics; for tho it is very well known, that as soon as the Sweat breaks out, Restlessness and other Symptoms, vanish immediately, and an Apyrexia succeeds, and therefore of consequence it must be indulged a little, at least not hinder'd, when the Fit is going off; yet it is very evident, that if Sweat be forced more than it should, the Fever which intermitted will prove continual, and the Life of the Sick is in a hazardous condition; and one is saved and the other dies; the reason is this, unless my Conjecture fails me, viz. that this profuse Sweat, when it exceeds the degree of the febrile Matter, exalted so far by the heat of the Fit, as that part of it answering to one Paroxysm may be ejected, it wastes the rest of it in inflaming the Blood. Therefore whilst I consider'd how ineffectual this Method was, and also other Evacuations, that is, Bleeding and Purging, both whereof by relaxing the Tone of the Blood, protract the disease, the Peruvian Bark gave me the most certain hope; concerning which I can safely say, notwithstanding the Prejudice of the common People, and of some of the Learned, I never saw, nor could reasonably so much as suspect any mischief would happen to the Sick from the use of it: only they who have used it a long while, as I have shew'd in the Chapter of a Rheumatism, are sometimes subject to a Rheumatic Scurvy; but this very rarely happens on this Account, and when it does, it is easily cured by the Remedies there prescribed. And truly, if I were as well assur'd of the duration of its Effects, as I am of its Innocence, I should not doubt to give it the first place, among all Medicines that are yet known: for it is not only found to be of excellent Virtue in this Disease, but also in the Diseases of the Womb and Stomach; so little reason has any one to complain of the Unwholesomeness of it.

But the said Bark has got an ill name, I suppose for these Reasons chiefly:

First, because all the dreadful Symptoms that attend an Ague, when it has tormented a Man a long time, are imputed to the Bark, when he has scarce used it once. Secondly, because many suppose, seeing it drives away the Disease by an occult Virtue, and not by sensible Evacuation, that the Matter causing the Disease, which should have been cast out, is shut up by the astringent Virtue of the Bark, like an Enemy within the Walls ready to give new Disturbance, and that the Patient is not quite free, for he drags his Chain after him still. But these Men do not consider, that the Sweats, which come at the end of the Fit, have cast off all that, that was gathered on the well Days, there remaining only the Seeds of the Disease to be ripened in time, and that the Bark pursuing the flying Fit (when all the Provision or Sustenance of the Disease which should have been sent in, is intercepted) cannot be said to retain that in the Blood, which cannot be found there, unless in Embryo, and therefore must not be thought guilty either of those Fits, or Obstructions which are commonly objected.

But by what means do we find that the Bark drives away Agues, by its astringent Faculty? He that would prove this, must necessarily first produce other Astringents indu'd with the like Virtue. Indeed I have try'd the strongest of them, but could never yet obtain my end; yea it cures some, who after the taking it, go as often to stool, as if they had taken a strong Purge. But when all is said, it is the truest Wisdom for every one to keep within his due Bound: but if any one will deceive himself, and think he is indu'd with other Faculties, than what are subservient, either to natural Religion, that is, that due Veneration be given to God, the Maker and Governor of all things, with the profoundest Prostration of Mind, which he of right deserves; or to moral Philosophy, that he may exercise Virtue, and become serviceable to human Society; or lastly to the Medical, Mathematical, or some other Mechanical Trade, which are beneficial to Mankind; let this Man first draw an Hypothesis from the natural School-Philosophy, whereby he can explain but only one specifick difference of things in Nature; for instance, Let him give a Reason why all Grass is every where found to be green, and never otherwise, and the like. If he can do this, I will readily subscribe to his Judgment; but if not, I will not fear to say, that all a Physician's Care and Industry should be bestowed in searching out the History of Diseases, and in using those Remedies, which, Experience being his Guide, are able to cure them, ever observing that Method which right Reason, founded not on speculative Imagination, but the right and natural way of thinking shall dictate. I will therefore briefly set down what I have learned by Practice concerning the Method of giving the Bark.

The Peruvian Bark, which is commonly called the Jesuits Pouder, about 25 Years ago, if I remember well, first became famous at London for curing Agues, and especially Quartans; and indeed for very good reason, seeing these Diseases were rarely cured before by any other Method or Medicine: wherefore they were call'd *Opprobria Medicorum*, and were truly a Reproach to Physicians. But not very long after it was damn'd for two Reasons, and those no small ones, and so was wholly disus'd. First, because it being given a few Hours before the Fit, according to the receiv'd custom of that time, it sometimes kill'd the Patient; and so I remember it happen'd to a Citizen of London, one Alderman Underwood, and to Captain Potter, an Apothecary in Black Friars: this Tragical Effect of the Pouder, tho very rare, did yet deservedly withdraw the best

Physicians from the use of it. Secondly, because tho the Patient was rid of his Fit by it, which would otherwise have come, and it seldom fail'd, yet within fourteen Days he relapsed; that is, when the Disease was new, and had not spent it self by length of time. Most Men being sway'd by these Reasons, quite cast off the hope they had formerly conceiv'd of this Pouder, neither did they so value the keeping off of a Fit for a few days as to endanger their lives by taking the Pouder. But having for several Years since seriously consider'd with my self that the Virtue of this Bark was not common, I was confident Agues could better be cured by no other Medicine than this Herculean one, if it were used with care: therefore I consider'd a long time how I might prevent the danger impending from the Pouder, and the Relapse, which followed in a few days, which were the two Inconveniences to be avoided, and by the help of it to promote the Patient to a degree of perfect Health.

First of all, I suppose, the Danger that was threaten'd did not so much proceed from the Bark, as from the unreasonable Use of it: for when great store of febrile Matter is gather'd in the Body on the Days of Intermission, the aforesaid Pouder, if it be taken immediately before the Fit, hinders the morbidick Matter from being ejected according to Nature's Method, that is, by the Force of the Fit; and being, contrary to all Reason, shut up, usually endangers the Patient's Life. Now I reckon'd, I could prevent this Mischief, and also put a stop to the breeding of febrile Matter a-new, if after one Fit is off, I presently gave the Pouder, that the following might be stop'd; and if on the Days of Intermission at set times, I repeated now and then the same till a new Fit were coming, I might gradually, and therefore safely, thorowly tinge the Mass of Blood with the salutiferous Virtue of the Bark.

Secondly, since the Relapse, which usually happens within fourteen days, seem'd to be occasion'd because the Blood was not sufficiently saturated with the Virtue of the Febrifuge, and for that reason was not efficacious enough; therefore I thought nothing would be so good for preventing a Relapse, as the Repetition of the Pouder at due distances, before the Virtue of the preceding Dose was quite spent, tho the Disease at present was quell'd.

My Mind, therefore, sway'd with the weight of these Reasons, dictated to me the Method I now use: Being call'd to one ill of a Quartan Ague, suppose on a Monday, if the Fit is to come the same Day, I meddle not, but only put him in hopes that he shall be freed from the next; and therefore the two well Days, that is, Tuesday and Wednesday, I gave the Bark in the following manner. [These details are here omitted.]

On Thursday, at which time the Fit is fear'd, I order nothing, because usually none comes; the Relicks of the febrile Matter being despumated, and ejected out of the Blood by the usual Sweats, which compleated the preceding Fit; and the gathering of a new Minera, or Fomes, being prevented by the repeated use of the Pouder of the Days between the Fits.

But however, lest the Disease should return, which was one of the foresaid Inconveniences, on the eighth Day precisely after the Patient had taken his last Dose, I certainly gave him the same quantity of the said Pouder, that is, one Ounce divided into twelve parts, in the same Method I gave the former: but tho the Bark once repeated in this manner often cures the Disease, yet the Patient is not wholly out of danger, unless he follows his Physician's Directions, when he prescribes him the same Method at the same distances, a third or fourth

time; especially when the Blood has been weaken'd with some preceding Evacuation, or the Patient has unadvisedly exposed himself to the cold Air.

Sydenham's observations illustrate the empirical method at its best; namely, when it is used to furnish the stuff for rational extensions. The value of the empirical method in general consists in its basis of experience of tangible observations. In medicine it has the additional value that it emphasizes clinical contact. The laboratory is indispensable in medical science, but in every case the final experience must be obtained directly on the subject to which it is to be applied in the clinic; or else the experience runs danger of becoming hazardous deductions.

As with cinchona, so in other things, the empiric method, the method of unreasoned experience, is a good start; but it is by no means the only possible start; it is not always applicable or profitable, and it should never be final.

Empirical experience opens up a field, but does not exhaust it; it prospects and locates gold, and picks up a few nuggets from the surface; but it cannot follow the vein. It starts an inquiry; but if this is to be continued and expanded, thought and planning become necessary, and thus the empiric merges quickly into the rational scientific method of experimentation.

Sydenham saw beyond the mere empiric experience that cinchona is good for malaria. He looked for the mechanism, and showed that it is not due to astringent action, but peculiar to itself. He noted that relapses will occur, and by reason and experiment he found that these are prevented if the drug is repeated for a time. This illustrates the task of scientific medicine: to subject the data of the experiences of empiric medicine systematically to critical tests; and if they are confirmed, then to attempt to learn more about them, so as to be able to improve upon them. Such scientific investigation may take many directions, as we shall attempt to illustrate by the cinchona alkaloids. The chronologic order in which these are followed is generally determined by extraneous and accidental circumstances.

THE PLANT CELL, MASTER ARTIST IN CHEMISTRY

One of the most important directions of medical research, especially since the development of organic chemistry, is the

attempt to produce more powerful and more useful therapeutic agents artificially. These attempts have led to many important discoveries in various directions; but it may be confessed at once that chemists have not yet succeeded in improving upon the anti-malarial efficiency of the natural cinchona alkaloids; indeed, they have not even succeeded in remotely approaching it. In this respect, the cinchona alkaloids are illustrative of the superior genius of the living cells of plants, animals, and bacteria, for synthesizing substances of strongly marked pharmacologic actions. The silent laboratory of nature beggars the proud achievements of organic chemistry. The vast number of artificial compounds that have been synthesised show relatively few pharmacologic actions of any originality. Their properties are along a few stereotyped lines; and those with distinctive actions are generally direct imitations of the natural agents. On the other hand, organic compounds that occur naturally exhibit a great variety of actions. It appears as if cellular synthesis is much more likely than is laboratory synthesis to hit upon marked and distinctive pharmacologic properties. This may be attributed in part to the greater originality of structure and design in the cellular laboratory. The inventions of the synthetic chemist are apt to follow a restricted number of patterns, determined largely by the ease of the synthesis, by fashion, etc. The cellular laboratory is not bound by such "school-patterns," and is therefore able to exhibit a greater boldness of conceptions, resulting in a greater variety of structure, and thus a greater variety of actions is possible and probable. However, this is not all, for the proportion of active compounds is too high to be purely accidental. With the alkaloids, for instance, almost every one has pharmacological actions, many being highly distinctive, that is, with a very selective mechanism. This holds still more for internal secretions. With these it may perhaps be attributed to evolutionary adaptation; but this explanation does not apply to the alkaloids, for the anti-malarial action of quinine, the tetanizing action of strychnine, the parasympathetic paralysis of atropine, and the uterotonic action of ergotamine are of no use whatever to the plants, and could not therefore have been developed by selection. The plants doubtless have some other use for these alkaloids; but

the mystery is that they should also have these very characteristic effects on animal cells. The explanation is probably analogous to that of the optical activity: Substances elaborated in the laboratory of the living cell carry the impress of this laboratory, and fit into the pattern of its activity, and are therefore more likely to engage in the activity of the cellular laboratory than are substances formed at hazard by the chemist. This need not be conceived as the impress of a mystical living force, for these substances can be reproduced artificially.

In some such manner, then, the cells of the cinchona tree elaborate a series of congeneric alkaloids, of rather wonderful architecture, which are as distinctively characteristic of the genus *Cinchona* as are its leaves or flowers. Why they are formed and how they are formed, and why they rather than nicotine or salicin, these are problems of the intimate nature of cell metabolism which we do not in the least understand, any more than why the thyroid gland forms thyroxin and the suprarenal gland forms epinephrine, and not the reverse. We do not know, but there is little doubt that it will be known in time. So far we have only learned by strictly empiric methods that the quantity and the relative proportion of the plant alkaloids may be modified, chiefly by selection and breeding, but to some extent also by the general conditions of nutrition and growth, especially through fertilizers. In brief, by the same methods which modify the colors and the perfumes of the flowers and fruits, the percentage of sugar in the beets, and the resistance to temperature, or drought or disease.

Perhaps, when the nature of the process is better understood, the problem may be attacked more directly and more rationally, and this would be a great achievement scientifically; but it is doubtful whether the yield of alkaloids could materially surpass the amount that has been reached by the empirical selection. The 13.5 per cent of quinine which may exist in the bark is really an astonishing quantity. Evidently, it must be present in insoluble form; perhaps as a storage-depot of nitrogenous material, much as the fat depots in animals and plants function as storage depots of energy. In that case, its peculiar and specifically selective action against malaria is merely an accidental, adven-

titious side-action, somewhat on a level with the property of castor oil which makes it a valuable lubricant for aeroplanes; or the property of starch to be colored blue by iodine. The starch-iodine reaction happens to have no particular relation to human welfare, whilst the quinine-malaria reaction is of supreme importance. It is time that we turn our attention to this reaction.

THE DAWN OF CHEMO-THERAPY

The extensive pioneer work of Ehrlich in the field of chemo-therapy tends to create the impression that he invented the subject. He did indeed invent the name and he brought the subject into the field of consciousness, but, as a matter of fact, chemo-therapy was invented by Cinchona; and this is still a perfect exemplar of the classical chemo-therapy in the Ehrlich sense, the treatment of infections by specific chemical agents, within the body. Essentially all that has been found out about the principles of chemo-therapy was already known from the cinchona-malaria reaction; but until Ehrlich came, the knowledge was purely empiric, and therefore disorderly, confused, and irrational, so that its significance could not be appreciated. Although Ehrlich's theories were not adequate and were sometimes misdirected, he deserves the credit of creating the point of view of chemo-therapy as a coherent entity, and thus opening the whole field to systematic and rational investigation.

Ehrlich's conception of chemo-therapy was an agent with high toxic affinity for the parasite, and low toxicity for the cells of the host; with the ideal that a single dose of the drug would kill all the parasites, and so eradicate the disease at one stroke. The effects of quinine against malaria come nearer to realizing this ideal in the human subject than perhaps any other chemo-therapy; for a single dose generally causes the complete disappearance of the plasmodia from the blood. It is true that often they may return unless the administration is continued, but this holds true also for all other instances of chemo-therapy. It could be made consistent with the Ehrlich conception of a direct parasitocidal action by the simple assumption that some of the plasmodia happen to be resistant to quinine, personally or through a stage of this developmental cycle; or more probably, that they happen

to be lodged in situations which the quinine does not reach in adequate concentration; for instance, in closed capillaries. On closer examination, these explanations are not quite as satisfactory as they sound, and supplementary assumptions become necessary, which are rather too far-fetched, too artificial, too forced, to be convincing. However, the chief difficulty with the primitive Ehrlichian concept of chemo-therapy, as direct parasitocidal action, is the low parasitocidal value of these agents outside of the body. This holds for the arsphenamines and mercury and iodides against the treponema; of the arsenicals against trypanosomes; of emetine against entamebas; and of many other chemo-therapy reactions that have been amenable to investigation. In every case, the concentration required to kill the parasite outside of the body appears much higher than the concentration that can be conceived to exist in the blood stream. In the case of quinine, the current method of treating cerebro-spinal syphilis with inoculation of the plasmodia gives a convincing method of testing this subject. It has been found that blood incubated for twenty-four hours with quinine (1:10000) is still capable of producing malaria; while the concentration of quinine in the blood could probably never have been maintained higher than 1:60000. In the case of the organic arsenic compounds, the difference has been attributed to the transformation into more effective compounds in the body. This does play a part, but it is doubtful whether it is the whole story. In the case of the alkaloïds, emetine and quinine, the assumption of toxic transformations is so unsupported by the chemistry of these agents that it appears improbable; and since the phenomena in their general course are so very similar to those of chemo-therapy by the metals, it appears probable that these depend on some other element than direct parasitocidal action.

AWKWARD FACTS AND POLISHED FANCIES

The solution of the puzzle of chemo-therapy has therefore been sought in other directions; but so far these efforts have not gone much beyond the stage of speculation. Decisive experiments are difficult to devise and to carry through. It is a field which requires the coöperation of immunology and pharmacology. The

vogue of malaria inoculations holds particularly favorable opportunities of harmless experimentation on a relatively simple and clean-cut chemo-therapy reaction. If the occasion is fully utilized, cinchona may render another great service to scientific medicine. However, the facts that are already known about the cinchona alkaloids are helpful in weighing the various theories of chemo-therapy. We have discussed how they tend to render the explanation of toxic decomposition inadequate. We may briefly review their bearing on some of the other theories. One of the oldest theories, far older than Ehrlich's, held that the "alteratives" stimulate the resistance of the cells in general, and so help them to overcome the disease or infection. The theory is so vague, so indefinite, that it is almost meaningless; but quinine has so little effect on "cells in general," that it could scarcely be imagined to increase their resistance. Moreover, the malarial invasion is so strictly confined to the red blood cells that "general resistance" would have little application.

A modernized and somewhat more definite version of the resistance theory is that the agents stimulate the production of immunizing substances by the cells. It would seem, however, that the effect of quinine is far too prompt to give opportunity for the manufacture of antibodies, which is a rather slow process.

The next suggestion is that of the sensitization of the parasites to the natural immune substances of the blood and tissues. The prompt action again suggests that the effect must concern the blood rather than the tissues; and again the failure of the quinine, in reasonable concentration, to kill the parasites in the shed blood, as shown by inoculation experiments, indicates that this is not the mechanism.

MOLECULAR STRUCTURE AND SPECIFICITY

Another phase of the puzzle is the high degree of specificity of the cinchona alkaloids. Chemically, these are all minor modifications of a fundamental structural pattern, consisting of a quinoline ring and a piperidine derivative, "loipon," linked together by a CH.OH (secondary alcohol) group. From the chemical standpoint, such a structure does not seem to suggest unique properties, but this merely reflects our ignorance of the

qualitative relations of chemical structure and pharmacological action. Chemists have prepared an abundant variety of derivatives of the two fundamental components of quinoline and of piperidine. Many of these reproduce various of the non-specific actions of quinine: the general antiseptic action; the analgesic and antipyretic effects; local anesthesia; depression of muscle and heart, and so forth; but not one of these numerous compounds possesses in the slightest degree the particular anti-malarial action. For this, it is necessary to have the particular type of quinoline and piperidine derivatives linked together in the particular way by the CH.OH group. Given this particular pattern, many changes may be made in the side-chains without destroying the anti-malarial action. The different cinchona alkaloids constitute such derivatives, and others can be prepared artificially. Their anti-malarial action differs only quantitatively and in rather minor degree. However, any substitution in the linkage group, CH.OH , is apt to destroy the anti-malarial action altogether. Of course, this group is not anti-malarial in itself, and we are quite ignorant as to why it should be an indispensable condition of this action. The structure therefore does not furnish us with the key to the problem. All that we can say is, that there is a high degree of specificity in the structure as well as in the chemotherapeutic results.

COLLOIDAL AND PHARMACOLOGICAL SPECIFICITIES

The strict specificity of the cinchona alkaloids suggests that we may have gone in the wrong direction, by envisaging the quinine-malaria reaction as merely a particular manifestation of a universal conception of chemo-therapy; and that we should attempt to conceive it as a quite unique phenomenon; that we should seek its explanation in some distinctive pharmacologic properties of the cinchona series rather than in general conceptions of chemo-therapy. We shall find that the pharmacology of the cinchona series does reveal some quite unique features. The first of these goes back to colloid chemistry: Quinine tends to condense on the surface of solutions, or at the interface, to such a degree that it forms rather rigid films. If a tough film were formed on the blood corpuscles, this might protect them mechan-

ically against the entrance of the parasites. However, this is merely a speculation without experimental support; for it has not been shown that the corpuscles are mechanically toughened, for instance, that their fragility to shaking, etc., is modified; nor does it follow that a purely temporary obstacle to penetration would have such a lasting effect on the parasitic invasion. We do not know.

It would also be conceivable that the quinine may condense on the parasites and thus hinder the movements that are necessary for their penetration into the corpuscles. This, too, is practically pure speculation.

The interface condensation would produce alterations in the colloidal properties of the blood; for instance, it is said to arrest the Brownian movements. Since immune-reactions are essentially colloidal interactions, this property of quinine may lead us back directly to immuno-therapy. At least, it suggests new lines of investigation of the effects of quinine on the colloidal characters of the blood, and on its effects on immune-reactions, precipitins, lysins, etc. However, the inefficiency of quinine in infections other than malaria again renders such generalized explanations improbable.

Another characteristic of the cinchona alkaloids is the peculiar interference with certain kinds of enzyme reactions. This is probably also based on their colloidal disturbance. These enzyme inhibitions show considerable selectivity which would be more consonant with the specificity of the anti-malarial action. This could then be conceived as interference with a metabolic process that is essential to the developmental cycle of the plasmodia. This sounds rather plausible, but experienced investigators have learned to beware of plausibilities until they have been tested. The difference between speculation and experimentation is that between dreaming and doing. Only by combining these can real progress be assured.

The antipyretic action of quinine offers another possible approach of the malarial interaction. It is well known that fever affects immune reactions. Artificial hyperpyrexia is used, for instance, against cerebro-spinal syphilis, when its location renders it inaccessible to the ordinary drug treatment. It would not be

surprising if other invaders, such as the plasmodia, were favored by hyperpyrexia, and therefore hindered by antipyretics. Since other antipyretics are ineffective against malaria, this could not be a mere matter of temperature, but would involve the manner in which the temperature is reduced. This would not be an obstacle to the explanation, for the quinine antipyresis, at least under certain conditions, involves mechanisms which are not shared by other antipyretics. However, it is not known whether these peculiarities appear in the anti-malarial reaction, so that this also is no more than a suggestion.

An altogether different line of thought is opened by the allergic idiosyncrasies to quinine, the dermal and edemic reactions which are very emphatic and alarming in hyper-susceptible individuals, but which occur to some extent in most individuals under suitable conditions. These again lead us back to immune reactions; it may be conceived that the acute allergic reaction against quinine involves the mobilization of immune substances which are also detrimental to the plasmodia. Again, however, this is a mere plausibility, which runs foul of the fact that the anti-malarial efficiency is proportional to the dose of the quinine, and not to the degree of hyper-susceptibility; so that the patients with strong allergic reactions are at a strong disadvantage.

THE WAY OUT

The list of plausible theories of the anti-malarial reaction could doubtless be extended further, but it may as well be stopped, for it does not seem to bring us anywhere. Somehow, we appear to be on the wrong road, lost in a maze of blind alleys, which look promising but which end against a dead wall. What is the trouble? Simply this, that we have indulged in the old game of speculation, directing our eyes to distant clouds instead of watching the solid road at our feet. An occasional orientation by the stars is indispensable, for guidance and for inspiration; but substantial progress can only be made by careful and thorough exploration of the territory immediately at hand. This was the notable deficiency in the exploration that we have made. At every turn, the absence of exact facts forced us to sweeping generalizations which ended in contradiction, or, what is worse,

in vague plausibilities. We must retrace our steps and reform our method, and devote ourselves to the prosaic pursuit of facts, to subjecting the facile suggestions to the unrelenting test of critical experimentation. This offers the best chance of attaining the ultimate objective of understanding the nature of chemo-therapy; but even if it should fall short of this objective, it will enrich us with substantial knowledge, which is a lasting achievement in itself and which may lead to even greater things.

THE ROLE OF QUININE IN THE CURE OF MALARIA

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In the history of the development of knowledge of the action of quinine in malaria there is a portrayal of the struggles, difficulties, disappointments, and successes which have attended the efforts of Magendie and his followers to place the treatment of human disease upon a sound basis by the methods of experimental pharmacology. Incidentally there is revealed how painfully slow is the progress and how difficult it is to establish the exact role of a well-known and widely used drug in the cure of one of the most important diseases of mankind. Malaria has been successfully treated on an empiric basis for centuries. Its etiologic agent has been known for the past fifty years as a plainly visible protozoan parasite, readily accessible to detailed morphological, and, within limits, cultural study. Innumerable clinical studies of the action of the drug on human beings have been made. Within the past ten years it has been possible to observe the course of experimentally produced infections in human beings under carefully controlled conditions. Ever since Ross and MacCallum did their pioneer work it has been realized that a closely related infection of birds afforded opportunity for valuable laboratory experiments. Yet knowledge of the exact role of quinine in the cure of malaria is still fragmentary. It is not our purpose here to review systematically all of the contributions to this subject, but rather to indicate the results achieved by different lines of investigation and to take stock of the present status of our information.

STUDIES IN CHEMO-THERAPY

One of the leaders of the embryo science of pharmacology in Germany during the nineteenth century was Karl Binz (1832-1912). In 'Experimentelle Untersuchungen über das Wesen der Chinin Wirkung' published in 1868, leaving the realms of pure empiricism and mysticism which surrounded the use of "Cardinal's Bark" and "Jesuit Powder," he attempted to give a rational explanation for the action of the chemical substance which Pel-

letier and Caventou had extracted from cinchona alkaloids in 1820 under the name of quinine. With prophetic acumen he advanced the opinion that malaria was caused by some low form of animal life, and that the curative action of quinine was due to its direct effect upon this micro-organism. He attempted to support this hypothesis by an experimental study of the effect of dilute solutions of quinine upon many species of infusoria and demonstrated its inhibitory effect upon these low forms of animal life.¹

His studies seem to have received little attention until Laveran actually discovered the plasmodium of malaria in 1881. The noted French army surgeon later confirmed the hypothesis which Binz had advanced by showing that when a 1:1000 solution of quinine was added to a preparation of malaria blood, observed under a microscope, the motility of the plasmodium was immediately arrested. On the basis of this observation and the known therapeutic effectiveness of quinine in malaria, Laveran asserted that, "it is because it destroys the parasite that quinine causes the disappearance of the manifestations of paludism."

This unequivocal statement from so noted an authority carried conviction to the medical world. The pharmacologists pointed with pride to this demonstration of therapeutic effectiveness which could be so clearly explained as due to a *direct action of the drug upon the parasite*. This conception, together with observations on the selectivity of dyes for certain body tissues, led Paul Ehrlich to evolve his famous side-chain theory of drug action in parasitic diseases, and twenty years later when he read the treatise of this same Alphonse Laveran upon 'Trypanosomes et trypanosomiasés,' in which were reported studies of the effect of arsenic injections upon mice infected with mal de Caderas, there was placed in his hands a parasitic infection of laboratory animals which served as the instrument for his epoch-making experiments in chemo-therapy. These studies were the starting point for that brilliant advance in the rational use of chemical compounds in the treatment of infections which

¹ This same method,—i. e. minimum lethal concentration against *Paramoecium caudatum*,—has recently been used in the selection of drugs for test in the cure of malaria by Hegner, Shaw, and Maxwell.

have contributed so richly to the relief of human suffering during the past two or three decades.

Influenced by this logical and satisfying explanation of the action of quinine, several eminent investigators searched for evidence of its effect upon the malarial parasite by studying changes in motility and in morphology in fresh and stained blood preparations obtained from patients subsequent to the administration of therapeutic doses. These classical researches have been widely quoted and need not be reviewed in detail here. In the case of *P. vivax*, Golgi, Romanovsky, Mannaberg, Ziemann, Craig, and others have described, with some disagreement as to histological detail, changes in motility, morphology, and staining characteristics which they interpret to be evidence of a direct effect of the drug upon the micro-organism within the red cell, particularly upon the younger forms, but evident in all stages of development. Similar changes in *P. malariae* could not be found by Antolisei and Golgi, but were evident to Mannaberg and Craig. Marchiafava and Bignami could not find them in stained preparations of *P. falciparum*, but Craig thought that detectable differences were revealed by proper technique.

Some years later Bass (1922) attempted to obtain evidence of direct action on the intra-corporal stages of *P. falciparum* by studying the effect of a dilute solution of quinine upon parasites in tissue culture. To a culture containing large numbers of ring forms in red cells he added an amount of quinine dihydrochloride sufficient to effect a concentration of 1:4000. After five hours of incubation, the parasites in preparations made from the quinine culture appeared to stain poorly and to have been arrested in development as compared with preparations made from a control culture to which no quinine had been added. The tentative inference was drawn that quinine in therapeutic proportions prevents the growth of malaria plasmodia *in vitro*. This type of experiment is open to the objection that a great variety of chemical substances, totally without value in the treatment of malaria, would have a similar effect if added to tissue cultures of plasmodia.

Admitting that quinine might be effective against the intra-corporal stages of development of *P. vivax*, most clinicians taught on the basis of the observations which have been recorded

that the chief effect of the drug was registered upon that stage of life cycle just after sporulation has occurred and while the merozoites were free in the blood serum attempting to penetrate new red-cells. Thus we find the following statement in Osler's 'Principles and Practice of Medicine.'² "Experiment has shown that the parasites are most easily destroyed by quinine at the stage when they are free in the circulation,—that is, during and just after segmentation. While in most instances the parasites of the regularly intermittent (tertian) fevers may be destroyed even in the intra-corpuscular stage, in aestivo-autumnal fever this is much more difficult." I have been unable to find record of an experiment in which the vulnerability of the merozoites in the blood stream to the action of quinine has been definitely demonstrated, although, granting direct action of quinine on the parasite in the blood circulation, one would expect this to be the case.

Depending upon the view which was held and because of the failure of quinine in some instances to effect a permanent cure, various systems of administration were advocated by authorities all over the world, with impressive figures based upon clinical experience to show the high percentage of successes. The interesting point is that, irrespective of the theory upon which based, most of these systems were effective, provided the drug were used in sufficient dosage for a sufficient period of time.

As usual, however, there were the cautious few who tried to keep all the facts in mind and not be carried away by a plausible hypothesis. These few maintained that the exact mechanism of cure was not yet clear. There was a paucity of exact knowledge and a plethora of speculation. Reviewing critically the available information certain fallacies of reasoning were apparent. It was pointed out, for example, that the specificity of quinine in the treatment of the disease malaria does not necessarily imply that its effect is registered directly and exclusively on the parasite in the blood stream; that, while quinine is undoubtedly a proto-plasmic poison *in vitro*, the same quality is possessed by many other chemicals, the arsenic derivatives for example, which have little or no value in the treatment of malaria *in vivo*; that

² Osler and McCrae. 9th ed. New York, 1923.

the existence of evidences of degeneration of the parasite in histological preparations of the blood made subsequent to the administration of quinine does not necessarily imply that this degeneration is due to direct action of the drug upon the parasite, but might be due to an indirect interference with the normal growth and development of the parasite.

CLINICAL STUDIES OF THE CURE OF NATURAL INFECTIONS

During the World War, the lack of exact knowledge of the action of quinine in malaria came acutely to the fore. Military operations were seriously hampered and indeed jeopardized by massive infection of troops serving in Africa, Macedonia, Mesopotamia, Persia, and Saloniki. In spite of all that could be done in the field by the administration of quinine by all known methods and dosages, prophylactically and therapeutically, thousands of soldiers were invalided with chronic malaria. The gathering together of large numbers of cases under uniform conditions of military hospitals where continuous observation of each patient was possible over a considerable period of time afforded an unusual opportunity for carefully controlled studies of various methods of treatment, notably those of J. W. W. Stephens and his associates in the Liverpool School of Tropical Medicine, and of Acton and his associates at Dageshai, India. (These studies have been critically reviewed by Clayton Lane.³)

Without going into a detailed consideration of the evidence, the following points were established on a fairly firm basis:

1. None of the other drugs which had been suggested as valuable in the treatment of malaria approached quinine in effectiveness.

2. In spite of numerous reported failures of quinine, when the drug was actually swallowed, retained, and absorbed, in doses as large as 10 grains twice per day, disappearance of the parasites from the peripheral blood and subsidence of the fever almost invariably followed.⁴

3. Clear distinction must be drawn between a clinical recovery

³ Review with bibliography by Clayton Lane, *Trop. Dis. Bull.* vol. 21, pp. 849-859. November, 1924.

⁴ Fletcher, Wm. Notes on the treatment of malaria with the alkaloids of cinchona. London, 1923.

and a parasitic cure, the latter implying the complete elimination of all parasites from the body so that relapse does not occur.

4. No matter by what method or in what dosage given, quinine seldom, if ever, rids the body of all parasites; a few remain and may cause relapse after quinine is discontinued.

5. The plasmodium causing malaria does not acquire resistance to the drug; i. e., develop "quinine fastness,"—such as has been observed with trypanosomes and arsenic.

6. Recent (primary) infections are more easily cured by quinine than are old, chronic (repeated) infections.

7. It makes no appreciable difference when the drug is administered with reference to the chill, i. e., the time of sporulation of the parasite.

8. Quinine is more effective against the schizonts of *P. falciparum* than of *P. vivax* whereas for the gametocytes the condition is reversed. It is questionable whether it has any effect whatever on crescents.

9. Intravenous injection of quinine is no more effective in ridding the body of parasites than is oral administration, although therapeutic control may be obtained somewhat more rapidly by the former mode of administration.

These studies cleared up many mooted points. They gave no indication that the various systems and modifications of treatment which had been advocated by various authorities served any useful purpose. They emphasized the fact that knowledge of the role of quinine in the cure of malaria was so meager that there was no scientific basis for conclusion as to the most effective way of administering it. The cure of malaria was evidently dependent upon something more than mere contact between the drug and the parasite in the blood stream. Why, with the same dosage and method of administration, do individuals vary so widely in their response? Why were recent (primary) infections more easily cured than chronic (repeated) infections? Why was the intravenous injection of the drug in exactly determined amounts no more effective in ridding the body of parasites than the irregular and uncertain absorption of small amounts from the gastro-intestinal tract? These and other questions were not satisfactorily answered on the basis of a simple drug-parasite relationship in the peripheral blood.

STUDIES OF METABOLISM

The need for exact information of the fate of quinine after introduction into the body has long been appreciated and numerous authors have contributed to our knowledge. The main facts seem to have been fairly well established but many important details are still obscure.

After oral administration of therapeutic doses, the drug is absorbed mainly from the small intestine. It is carried to the liver where a variable amount is fixed and the balance passes on to the general circulation. In the blood stream it can be demonstrated only in minute traces. Morgenroth⁵ estimates the dilution as greater than 1:150,000. Ramsden, Lipkin and Whitley⁶ found the maximum strength of quinine to be 1 in 100,000 twenty-seven hours after its administration. Hatcher and Gold⁷ made estimations on twelve specimens averaging about 0.25 per cent of the total blood drawn from twelve patients after intervals of about thirty minutes in seven cases, and up to two days in others, following the administration of quinine in varying doses by mouth and intramuscularly. Quinine could not be detected in any single specimen of blood, but a trace was recovered from the combined extracts of all the specimens. These twelve patients took a total of 14,500 mgms. (940 grains).

After intravenous administration, if the drug be injected rapidly, a concentration as great as 1:20,000 may be obtained, but rapid elimination from the blood stream takes place. In the cat Hatcher found only minute traces present one minute after intravenous injection. Within three minutes after intravenous injection into a rabbit, Ramsden, Lipkin and Whitley found that 90 per cent had disappeared from the circulation. In studies made on eleven human cases treated by intravenous injections they found no direct correlation between the concentration of

⁵ Morgenroth, J. *Die Therapie der Malaria durch China alkaloide und ihre theoretischen Grundlagen*. Deutsche med. Wochenschr. vol. 44, pp. 961-965, 988-992. 1918.

⁶ Ramsden, W., Lipkin, I. J., and Whitley, E. On quinine in animal tissues and liquids with methods for its estimation. *Ann. Trop. Med.* vol. 12, pp. 223-258. 1918.

⁷ Hatcher, R., and Weiss, S. Studies on quinine. *Jour. Pharmacol. & Exp. Therap.* vol. 29, pp. 279-296. 1926; and Hatcher, R., and Gold, H. *ibid.* vol. 30, pp. 327-333, 347-350. 1927.

quinine in the blood and the rapidity of disappearance of the parasites. From the blood a certain amount, varying with the individual, but averaging about 35 per cent of the total amount administered, is eliminated by the kidneys through the urine within a period from 3 to 24 hours. Very little passes out in the feces unless there be a diarrhoea. The balance is fixed in the tissues. It appears to be stored in some tissues more than in others. The adrenals, for example, fix a much larger amount in proportion to their weight than do the liver, spleen, kidney, and bone-marrow. In the tissues it is slowly broken down, some having greater power to destroy it than others, and traces may be demonstrable for several days after administration has ceased.

It is apparent from these studies that quinine makes only a brief stay—a matter of minutes—in the blood circulation and is present here only in minute traces. It can be recovered in much greater concentration in certain tissues, in which it remains for days or weeks.

As to whether that portion which is found in the blood is partitioned more to the serum or more to the red cells there is some difference in results. That a certain amount is, however, absorbed by the red cells is definitely demonstrated by the work of Shaw and others.⁸ Moreover, Hegner, Shaw and Manwell have found that quinine and plasmochin have a higher partition coefficient (i. e. absorbed to a greater degree by red cells than by serum) than many other alkaloids and chemical compounds which have been tried and found to be less effective in the cure of bird malaria.⁹

Summarizing the histological, clinical, and metabolic studies which have been reviewed, one must admit that they fail to establish unequivocally:

1. A direct action of quinine on the parasite in the red cell or outside the red cell;
2. A direct relation between concentration of quinine in the blood stream and disappearance of the parasite.

⁸ Shaw, E. H. The absorption of chemical compounds by red blood corpuscles and its therapeutic significance in the treatment of malaria. *Jour. Hyg.* vol. 8, p. 583. 1928.

⁹ Hegner, R., Shaw, E. H., and Manwell, R. D. Methods and results of experiments on the effects of drugs in bird malaria. *Ibid.* pp. 564-582. 1928.

3. That the cure depends only or exclusively upon the parasite-drug contact.

On the other hand they strongly suggest that the mechanism is a more complicated affair and that other factors must be considered in the recovery of a human being from the infection.

STUDIES IN IMMUNITY

With the growing realization that recovery from malaria depended upon something more than a chemo-therapeutic reaction, increasing attention has been given the natural response of the body tissues to this infection.

It has long been known that adult natives of a malarious country were relatively resistant to infection and that children and new-comers were relatively susceptible. It is a common observation that some individuals may live in malarious regions for a considerable length of time, taking no precautions against infection, and never develop symptoms of the disease.¹⁰ It has been realized that latent infections relapsed when the host was subjected to some unusual experience,—change of climate or altitude, trauma, child-birth, and various other influences. It was also realized that among native peoples a great majority of infections must cure spontaneously, else large parts of the tropical population would have been wiped out.

Attempts to define more exactly the nature of this body defense date back to the early work in malaria pathology. Marchiafava and Bignami,¹¹ Celli, Golgi, Metchnikoff, Osler, Barker, Dock, Thayer, and others observed and remarked upon the phagocytic activity of mononuclear cells which could be found loaded with pigment in the lymph spaces, particularly of the spleen. Laveran had thought that this pigment was taken up only after fragmentation and death of the plasmodia, but Marchiafava and Celli observed phagocytes actually engulfing and destroying living plasmodia.

Metchnikoff, with his tremendous enthusiasm for the part played by the phagocytes in recovery from disease, seized upon this phenomenon to substantiate his hypothesis. He vigorously

¹⁰ Celli, A. *Malaria*. London, 1900.

¹¹ Marchiafava and Bignami. *Malaria*. Twentieth century practice. vol. 19. New York, 1900.

maintained that the chief body defense against malaria was phagocytosis and that either by engulfing and digesting plasmodia or by excreting products inimical to their growth, the phagocytes were responsible for spontaneous recovery. Others, while they admitted a role to the phagocytes, were unwilling to grant that they were the chief or only means of defense.

When Bass and Johns (1912) first evolved a technique for continuing the development of parasites *in vitro* through two or more generations, they remarked upon the great activity of phagocytes in such cultures. Large mononuclear cells were observed to engulf large numbers of red cells containing sporulating schizonts as well as devour the liberated merozoites.

In addition to this phenomenon, they inferred the presence of a lytic principle in the serum to account for the rapid disappearance of large numbers of the free parasites. This inference does not seem to have been sustained by later work, and the existence of parasitocidal activity of normal or immune serum is still unproved.

In like manner, although several authors have postulated the existence of malarial toxins and endo-toxins (paroxysmal toxins, Schilling, 1927)¹² to explain the occurrence of symptoms at the time of sporulation, and of the development of proper antibodies,—antitoxin or anti-endotoxin,—these substances still remain within the realms of speculation. The production of chills, fever, and other symptoms can be explained more simply on the ground of sudden liberation of a foreign protein by rupture of the red cells, and this conception is more in accord with present views of the underlying reactions to infection.

So far as present knowledge goes therefore, the chief agent of defense against the malarial parasite is the monocyte. It is but one step farther to link this defense with the reticulo-endothelial system. Among others Jaffé (1927) has pointed out that in patients dying of malaria the malaria pigment is most distinct in the reticulo-endothelial cells of the hemapoietic organs and produces a picture resembling vitally stained animals.¹³

¹² Schilling, C. Immunität bei Protozoenintoxicationen. Kollé, W. und Wassermann, A. Handbuch der pathogenen Mikroorganismen. vol. 8, pp. 95-140. 3rd ed. 1927.

¹³ Jaffé, R. H. The reticulo-endothelial system. Arch. Path. & Lab. Med., vol. 4, pp. 45-91. 1927.

Studies of bird malaria (MacCallum,¹⁴ 1898; Ben-Harel,¹⁵ 1923) have likewise indicated that fixed tissue phagocytes were largely concerned with the destruction of parasites. Moreover, the observations of W. H. and L. G. Taliaferro have produced a very interesting and suggestive picture of how the immunity mechanism works in the avian disease.¹⁶ What takes place after the infection of a canary with *Plasmodium cathemerium* is briefly described by L. G. Taliaferro as follows:

After the incubation period the asexual stages of the parasite are to be found in the peripheral blood in varying numbers during the entire course of the infection and undergo their cycle of development and reproduction at the same rate throughout. From the very beginning only a number of merozoites are viable; this probably represents a natural resistance of the host. During the first part of the infection relatively few parasites are killed, so that they accumulate in the blood, and give rise to the acute stage of the infection. Sooner or later, however, as the acquired resistance is built up, a large proportion of the parasites are killed. There may then be a temporary relapse, but, eventually, the destruction of the parasites equalizes or exceeds the number produced by reproduction, and the chronic period or low grade of blood infection ensues. In time, the destruction becomes so great that no parasites can be found in the blood (latent period), but their presence can be demonstrated by Whitmore's technique (i. e. by injecting blood into fresh, uninfected canaries). This continues until some condition, such as the injection of adrenalin, temporarily stops the destruction and the parasites accumulate again, causing a relapse.

Apparently two parasitocidal mechanisms are operative. The first is responsible for the constant death rate of most (about $\frac{2}{3}$) of the progeny from each asexual generation during the acute period and is identified with "natural resistance." The second is responsible for the very much increased death-rate which brings about a critical drop in the number of parasites in the blood, terminating the acute period and continuing throughout the remainder of the infection, except during the acute rise during the relapses. This is apparently an acquired resistance. Whether two different mechanisms are involved or whether the second is merely an enhancement of the first, is not yet clear, nor is it clear just how the death of the parasites is brought about. It seems

¹⁴ MacCallum, W. S. Notes on the pathological changes in the organs of birds infected with Haemacytozoa. Jour. Exp. Med. vol. 3, pp. 103-116. 1898.

¹⁵ Ben-Harel, S. Studies on bird malaria with relation to the mechanism of relapse. Amer. Jour. Hyg., vol. 3, pp. 652-685. 1923.

¹⁶ Taliaferro, W. H. The immunology of parasitic infections. New York. 1929.

probable, however, that the principal mechanism is phagocytosis, and the factors which render the parasite or the parasite-red-cell combination phagocytatable, and determine other qualitative or quantitative changes in the phagocytes available from the reticulo-endothelial system.

The mechanism involved in the recovery of man from infections with *P. vivax* and *P. falciparum* is probably much the same as that operative in avian malaria. Further elucidation of the exact nature of this mechanism must await more work. It is sufficient to point out here that *there is such a natural mechanism, that it can bring about a rapid disappearance of parasites from the blood and of clinical symptoms, and that it plays an important role in recovery irrespective of whether quinine be administered or not.*

STUDIES OF INOCULATION MALARIA IN THE TREATMENT OF GENERAL PARALYSIS

The discovery by Wagner-Jauregg of the favorable influence exerted by a malaria infection upon the course of general paralysis of the insane has given opportunity for many interesting studies and has resulted in many valuable recent contributions. Opportunity has been afforded to observe the course of the infection in human beings under experimentally controlled circumstances, and to use human beings to determine infectivity of mosquitoes and parasites under varied conditions.

The existence of natural and acquired immunity has been fully confirmed by these studies (Yorke and Macfie, S. P. James, P. Mühlens, Otto Kanders, and others.) In the first place, it has been repeatedly demonstrated that certain individuals are highly refractory to infection with malaria. For example, James¹⁷ found that 52 patients among 221 bitten by mosquitoes known to be infective failed to develop the disease. Many such individuals become infected when exposed a second time; some not until exposed a third time. Occasionally an individual is encountered who is not successfully infected even after four or five attempts.

In the second place it has been repeatedly observed that a primary inoculation with malaria is followed by a certain degree of immunity or allergy to subsequent inoculations. After recovery

¹⁷ James, S. P. Epidemiological results of a laboratory study of malaria in England. Trans. Roy. Soc. Trop. Med. & Hyg., Vol. 20, pp. 143-165. 1926-27.

from the first, if again inoculated, the second attack is less severe and of shorter duration. Numerous instances of spontaneous recovery without the administration of quinine have been observed after a primary attack, but are particularly common after a second or third. Indeed it has been the common experience in cases of inoculation malaria to find that comparatively small doses of quinine,—ten to sixty grains spread over two or three days,—is followed by disappearance of the parasite from the blood stream and clinical recovery, and that relapses are extremely rare. Why it should be so much easier to clear up experimental infections than to cure natural infections has not yet been satisfactorily explained. It is evident, however, that extremely minute amounts of quinine distributed throughout the body may be sufficient to turn the struggle in favor of the defensive mechanism.

Concerning the direct action of solutions of quinine on blood-parasite mixtures, two recent experiments are of considerable interest. In connection with their studies of methods of preserving malarial blood for inoculation, Mühlens and Kirschbaum performed the following experiment.¹⁸ They added 2 cc. of a 1:5000 solution of quinine hydrochloride in normal saline to an equal amount of defibrinated human blood containing tertian parasites. This culture was allowed to stand 12 hours at 37° C. and then injected subcutaneously into two human beings, both of whom came down with typical tertian malaria. In blood preparations made at the time of inoculation they were unable to find morphological evidence of damage to the parasites within the red cells beyond that which is evident in similar cultures to which no quinine had been added.

In a similar experiment in which the blood-quinine mixture was kept for 24 hours in the incubator the subsequent inoculation failed to infect. Experiments with neo-salvarsan gave similar results in the dilutions used, although this drug is known to be of no value in the treatment of malaria. These observations have been confirmed by Yorke and Macfie (unpublished).

¹⁸ Mühlens, P., und Kirschbaum, W. Weitere parasitologische Beobachtungen bei künstlichen Malariainfektionen von Paralytikern. *Archiv f. Schiffs- u. Tropen-Hyg.*, vol. 28, pp. 131-144. 1924.

From these experiments it would appear that, *in vitro* at least, some of the intra-corpuseular forms of *P. vivax* can withstand exposure of several hours to concentrated solutions of quinine. Giemsa (1927) objects, however, that the physico-chemical relationships which exist in the blood *in vivo* are quite different from those realized under the conditions of this experiment,—particularly the dilution of the blood with normal salt solution.¹⁹

This objection is largely met by the conditions of a similar experiment reported by James, Nicol and Shute.²⁰ Having demonstrated in their previous studies that the injection into man of sporozoites obtained from infected mosquitoes produced infection, they placed two mosquitoes infected with *P. vivax* in a 1:5000 solution of quinine bisulphate made up with human blood serum instead of salt solution. In this solution the salivary glands were dissected and teased up. One cubic centimeter of this solution was drawn into a hypodermic syringe, allowed to remain for fifteen minutes, and then injected subcutaneously into a human being. At the end of ten days, the patient had a malarial paroxysm and *Plasmodium vivax* was found in the blood. It is concluded from this experiment that quinine in this concentration did not destroy all of the sporozoites present in the blood serum during the fifteen-minute contact.

The lack of effect upon the sporozoite stage has been repeatedly confirmed by field experiments on the prophylactic value of quinine.²¹ It has been clearly demonstrated by Yorke and Macfie²² that the oral administration of small doses of quinine immediately before, during, or just after exposure does not constantly prevent experimental infection.

DISCUSSION

Although these experiments demonstrated that concentrated solutions of quinine would not completely destroy the infectivity

¹⁹ Giemsa, G. Ueber den Mechanismus der antimalarischen Chininwirkung. München. Med. Wochenschr., vol. 74, pp. 574-577. 1927.

²⁰ James, S. P., Nicol, W. D., and Shute, P. S. Note on new procedure for malaria research. Trans. Roy. Soc. Trop. Med. & Hyg., vol. 21, pp. 233-236. 1927-28.

²¹ McNabb, P. E., and Stewart, T. H. Experiences in quinine prophylaxis of malarial infections in Panama Canal Zone. Am. Jour. Trop. Med. vol. 7, p. 357. 1927.

²² Yorke, W., and Macfie, J. W. S. Observations on malaria during the treatment of general paralysis. Lancet, vol. 1, pp. 1017-1019. 1924.

of blood containing tertian schizonts and of serum containing sporozoites by direct contact in the test-tube, it does not necessarily follow that quinine is without direct or indirect effect upon parasites in the concentrations and under the conditions realized in the blood stream. Kroo and Schultz, in an interesting experiment, found evidence that the intravenous injection of dilute solutions of quinine into infected human beings were more effective than the injection of concentrated solutions. They suggest that there may be a critical dilution, as well as a critical concentration, in such therapy, like the "zone phenomena" exhibited by certain protective sera.²³

It is conceivable that quinine acts on the parasite, even though present in very minute amounts in the blood. The idea has been advanced particularly by Morgenroth, by Schilling and Boecker²⁴ and by Rona and Bloch,²⁵ that it is the extremely minute amount fixed by the red blood cells which is effective. The studies of Hegner, Shaw and Manwell (1928) on the effect of drugs in bird malaria have shown that, as compared with other closely related but less effective compounds, quinine and plasmochin have a high partition coefficient, i. e., are absorbed to a greater degree by the red blood cells than by the serum.

Granting this to be the active portion, there are still at least three possibilities as to its mode of action. First, the quinine may be taken up by the protoplasm of the plasmodium and exert a direct toxic effect in the sense of Ehrlich; second, it may damage or sensitize the red cell-parasite combination in such a way that it goes to pieces more readily before development is completed; or third, it may in some way alter the surface tension of the red cell and render it relatively impervious to penetration by the liberated merozoites, so that a larger and larger proportion perish with each sporulation. In other words, in the second and third instances it may possess a genesistatic, rather than a para-

²³ Kroo, H. und Schultz, F. O. Ueber die Bedingungen optimaler chemo-therapeutischer Wirkung. Deut. med. Wochenschr. vol. 53, pp. 1759-1760. 1927.

²⁴ Schilling, C. und Boecker, E. Ueber die Speicherung von Chinaalkaloiden in Blutzellen. Deut. med. Wochenschr. vol. 45, pp. 682-684. 1919.

²⁵ Rona, P., und Bloch, E. Untersuchungen über die Bindung des Chinins an roten Blutkörperchen und über die Verteilung des Chinins im Blute. Biochem. Zeitschr. vol. 121, pp. 235-258. 1921; and vol. 123, pp. 169-184. 1922.

siticial, activity, such as has been demonstrated for certain dyes in great dilution in contact with bacteria (bacteriostasis).

One can question but not ignore the histological studies of qualified research workers who have found definite evidence of damage to *P. vivax* schizonts following the administration of quinine. It seems to be a well-established fact that quinine is more effective against the schizonts of *P. falciparum* than against those of *P. vivax*, and that the reverse is true for the gametocytes. It is worth recalling in this connection that recent work on the closely related drug—Plasmochin—has proved beyond question that it has a direct selective action upon the gametocytes of both *P. falciparum* and *P. vivax*, having the power to devitalize and destroy them at some stage in their development.

It must be admitted, however, that it has not been proved beyond question that the portion of quinine which is free in the blood stream and absorbed by the red cells is the effective portion. Many authors have pointed out that the larger part of the quinine absorbed is fixed in various body tissues in the capillary bed of which it may exert its action on the parasites for a much longer period of time and in greater concentration than is possible in the blood stream. Furthermore, as the late Dr. H. R. Carter has pointed out, the ability of different individuals to fix quinine in the tissues, particularly in the liver, might account for individual variations in the response to the drug. It is evident that the fixation of a large proportion of the quinine in the liver, after oral administration, would affect very materially the balance available to fight the parasite in the general circulation and other parts of the body. It might account for some of the cases which appear to be "resistant" to treatment, and the obstinacy of old infections many times broken with quinine and relapsing. It has been suggested by Lipkin that quinine itself is inactive against the parasite, but that in contact with the liver cells or some other tissue a metabolite is produced which has the necessary qualities.²⁵ The existence of such a compound has not yet been proved.

It can be seen from the above considerations that our informa-

²⁵ Lipkin, I. J. On the distribution and destruction of quinine in animal tissues. *Ann. Trop. Med. & Parasit.* vol. 13, pp. 149-176. 1919.

tion is not yet sufficiently complete to permit the assumption that the cure of malaria by quinine depends entirely and solely upon a direct chemical action on the parasite. On the other hand, there is unequivocal evidence that man possesses his own defense mechanism against malaria; that this defense becomes greatly enhanced as a result of infection (acquired immunity); that this mechanism is capable under certain circumstances of ridding the body of parasites,—without quinine; that the chief factor in this defense at present known is phagocytosis by the mono-nuclears of the reticulo-endothelial system.

Shall we assume that the action of this mechanism and the action of quinine are two entirely unrelated and separate phenomena? Or is there some means of collaboration between the two agencies?

If quinine acts with the defense mechanism it would seem necessary to infer, with present knowledge, that it in some way promotes phagocytosis,—whether by mobilizing the monocytic cells, or by rendering the red cell-parasite combination more phagocytatable. It may of course act in both ways, that is, directly to destroy a large proportion of the parasites and so to leave only a few in the protected areas which can be readily handled by the phagocytes otherwise unable adequately to cope with the situation.

It is not our purpose here to support or defend any hypothesis of the role of quinine in the cure of malaria. To do so would be apt to cloud the issue rather than to clear it. We are still ignorant as to just what takes place, even in the case of this, perhaps the most valuable, drug which is possessed by mankind.

This review leads to the inevitable conclusion that the simple chemo-therapeutic conception of Ehrlich is not adequate to explain all the known facts with regard to the cure of malaria by quinine. It has been realized in this disease as in others in which chemical compounds have been found to be highly specific that *the human body is not a test-tube*. The reaction of the body tissues to the drug and to the parasite cannot be ignored. Quinine in some manner, directly or indirectly, destroys large numbers of parasites—perhaps the maximum service that can be expected of any drug, but in the end complete and final recovery must be

brought about by host's own body cells. The drug plays a role, even an important role, but its action cannot be divorced and considered entirely separate from those natural phenomena which are directed toward the same end. We have passed through the period of chemo-therapy and are entering the period of chemo-immunology.

